The Relationship between Plasma NT-proBNP Level and Pacing Mode in the Patient with Implanted Permanent Pacemaker

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Background and Objective: *Plasma BNP is current one of the prognostic markers for cardiovascular disease including congestive heart failure. The objective of the present study was to evaluate the level of plasma NT-proBNP in patients who have had permanent pacemaker implantation.*
Material and Method: *The clinical characteristics and the plasma NT-proBNP level were recorded and obtained from 284 patients with implanted permanent pacemaker followed-up at the Pacemaker Clinic, Siriraj Hospital. The factors associated with abnormal NT-proBNP level were analyzed.*
Results: *Among 284 patients who participated in the present study, 140 patients had NT-proBNP in normal range (level of < 300 pg/ml). 68 patients had NT-proBNP level between 300 to 900 pg/m/ and 76 patients had NT-proBNP level > 900 pg/ml. There were significant correlations between log NT-proBNP with patient's age, left ventricular ejection fraction and serum creatinine level with age and serum creatinine showing positive correlation and left ventricular ejection fraction having a negative correlation. From multiple regression analysis, three factors were associated with high NT-proBNP level: older age, serum creatinine level and ventricular based pacing. The patients with ventricular based pacing mode had higher NT-proBNP level than patients with atrial based pacing mode even after being adjusted for age and serum creatinine adjusted*
Conclusion: *In the patient with permanent pacemaker, three factors are associated with high NT-proBNP level. These are older age, serum creatinine level, and ventricular based pacemaker.*

Keywords: *Brain natriuretic peptide, Pacemaker, NT-ProBNP, Ventricular-based pacing*

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Pro brain natriuretic peptide (proBNP), which is released primarily in response to increased atrial and ventricular stress, is cleaved into physiologically active brain natriuretic peptide (BNP) and the N-terminal pro B-type natriuretic peptide (NT-proBNP)[1]. Plasma BNP is not only a tool in the diagnosis of individuals with congestive heart failure but is also helpful in the assessment of heart failure severity and prognosis[2-5]. There is evidence that ventricular pacing increased BNP level[6]. Furthermore, plasma BNP levels may reflect hemodynamic changes elicited by different pacing modes, whereas plasma BNP levels are significantly higher during ventricular based pacing mode than during atrial based pacing pacing mode[7,8].

The objective of the present study is to evaluate the level of plasma NT-proBNP in the patients who have had permanent pacemaker implantation and to determine the factors associated with high NT-proBNP level.

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Material and Method

From November 1, 2004 to April 30 2005, any patients who had visited the Pacemaker Clinic at Siriraj Hospital for pacemaker check up were invited to participate in the present study. The patients were enrolled in the present study only after the written informed consent was given by the patients or their representatives. Exclusion criteria include: 1. Patients who refused to participate in the study 2. Patients with baseline serum creatinine of $\geq$ 2 mg/dl 3. Patients who had congestive heart failure or acute coronary syndrome within one month. Baseline characteristics of the patients, including sex, age, serum creatinine, atherosclerotic risk factors, medication and echocardiogram parameters, were recorded. The pacing mode was programmed with parameters as follows: the dual

chamber pacemaker was programmed to DDD(R) with long atrioventricular delay to ensure intrinsic ventricular contraction. The single chamber pacemaker was programmed to VVI(R) at a range of 50-120 beats per minute. All pacemaker interrogation was performed at Her Majesty Cardiac Center, Siriraj Hospital. Left ventricular ejection fraction by echocardiogram was assessed with modified Simpson's method.

The present study protocol was approved by the Institute's Ethics Committee Siriraj Hospital Mahidol University.

Measurement of plasma NT-proBNP level

The determination of N-terminal pro B-type natriuretic peptide in the present study was performed using immunoassay technique. Five milliliters of blood was collected with standard tube and sent to central laboratory within 2 hours. The system used was the Roche Elecsys 1010/2010 and Modular Analytics E170 (Elecsys module) immunoassay analyzers with electrochemiluminescence immunoassay method. The normal value of NT-proBNP level was $\leq$ 300 pg/ml.

Statistical analysis

Measured data are presented as mean $\pm$ SD whereas categorical data are presented as number and percentage. Log transformation of NT-proBNP level was used for analysis and the term NT-proBNP means log value of NT-proBNP in this article. The log NT-proBNP was used in calculation and analysis instead of NT-proBNP because of non normal distribution of NT-proBNP data. The level of NT-proBNP was log-transformed before any calculation in the present study. Log NT-proBNP were proved to have normal distribution ($p = 0.315$) by using Komolgorov-Smirnov test. Patients are divided into 3 groups (normal moderately elevated and markedly elevated level of NT-proBNP). NT-proBNP range of 1-300 pg/ml is classified as normal, 301-900 pg/ml = moderately elevated level of NT-proBNP, markedly elevated level of NT-proBNP means level > 900 pg/ml. Association between patient characteristics and level of log NT-proBNP are analyzed using ANOVA for measured variables. Chi-square test was used for assessing the association between categorical characteristics and NT-proBNP group. Differences of characteristics between the 3 groups of NT-proBNP level were assessed by ANOVA with Bonferroni post hoc test. To evaluate the relationship between NT-proBNP and patient characteristics, correlation coefficients are computed using Pearson's correlation coefficient method. In all analyses performed, a p-value of less than 0.05 is considered as statistical significance. All tests are performed by 2-sided test. Multivariable analysis was done by using multiple logistic regression, any characteristics with p-value < 0.20 from univariate analysis were used as independent variables in logistic model. An absence of factor such as no HT is coded as '0' where presence is coded as'1', atrial based pacing mode is coded as '0', and ventricular based pacing mode is coded as '1'. Multiple logistic regression is done by stepwise forward method. Odds ratio (OR) with 95% confidence interval (CI) were also calculated. An OR > 1 with $p < 0.05$ is considered to be an independent factor of high NT-proBNP level.

Results

There were 284 patients from 402 who agreed to participate in the study. One hundred and sixty five (58%) patients were female and the mean age was 64.32 $\pm$ 15.94 years. Most patients carried a normal left ventricular systolic function, with average left ventricular ejection fraction of 62.35 $\pm$ 14.85%. Baseline serum creatinine was 1.19 $\pm$ 0.54 mg/dl. Baseline characteristics of the patients are shown in Table 1.

Table 1. Patient characteristics

characteristics	Total (n = 284)
NT-proBNP level (pg/ml)	1,144.07 $\pm$ 3,397.35
Log NT-proBNP	2.52 $\pm$ 0.65
Age (yrs)	64.32 $\pm$ 15.94
Sex (female)	165 (58.0)
History	
HTN	50 (17.6)
DM	50 (17.6)
Dyslipidemia	75 (26.4)
Medication	
Statin	105 (37)
Beta blocker	103 (36.3)
ACEI/ARB	94 (33.1)
Pacing mode	
Atrial based	182 (64.1)
Ventricular based	102 (35.9)
Other findings	
LVEF (n = 136)	62.35 $\pm$ 14.85
Cr (n = 191)	1.19 $\pm$ 0.54

Continuous variables were reported as mean + SD, categorical variables were reported as frequency (%).
ACEI= angiotensin converting enzyme inhibitors, ARB = angiotensin receptor blockers, DM = diabetes mellitus, Cr = creatinine, HTN = hypertension, LVEF = left ventricular ejection fraction

The patients' characteristics were recorded and the plasma NT-proBNP level was obtained. Among 284 patients agreed to participate in the study, 140 patients had NT-proBNP level in normal range (level of < 300 pg/ml, group1). 68 patients were in group 2 with NT-proBNP level between 300 to 900 pg/ml (moderately elevated NT-proBNP level) and 76 patients had markedly elevated NT-proBNP level (Group 3 with NT-proBNP level > 900 pg/ml). Univariate analysis for the factors that were associated with abnormal NT-proBNP level showed age, serum creatinine level, left ventricular ejection fraction, DM, beta blocker use, and pacing mode were associated with abnormal NT-proBNP level. The detail of analysis was showed in Table 2.

With bivariate analysis of these clinical factors, there were significant correlations between log NT-pro BNP with patient's age, left ventricular ejection fraction and serum creatinine level. Age ($r = 0.0348$, $p < 0.01$) and serum creatinine ($r = 0.473$, $p < 0.01$) showed positive correlation and left ventricular ejection fraction ($r = -0.406$, $p < 0.01$) had negative correlation (Table 3). Using Multiple Logistic Regression, three clinical factors are found to have significant effect on BNP. These factors are age, serum creatinine level and ventricular pacing mode as shown in Table 4.

When compared to atrial based pacing mode, the patients with ventricular based pacing mode had higher level of NT-proBNP (log NT-pro BNP) as shown in Table 5. This difference persisted after age and serum creatinine adjustment (adjusted odds ratio = 4.86, 95% CI = 2.04-8.71, p-value = 0.004).

Discussion

The present study showed that the patients with ventricular based pacemaker had higher level of NT-proBNP compared to the group with atrial based pacing mode. The authors used log transformation of NT-proBNP level for calculation because of the non-normal distribution of the data. Three groups of NT-proBNP, according to the levels of < 300, 300-900, and

Table 3. Correlation coefficients between log NT-proBNP and patient characteristics

Patient characteristics	Correlation coefficient	p-value
Age (year)	0.348	< 0.01
Creatinine (mg/dl)	0.473	< 0.01
LVEF (%)	-0.406	< 0.01

Table 2. Association between patients' characteristics and abnormal level of log NT-proBNP by univariate analysis

Patient characteristic	NT-proBNP group*		p-value
	Normal (%)	High (%)	
Age groups (10 years)			< 0.001
Sex			
Male	36.4	47.2	0.065
Female	63.6	52.8	
HT	56.4	52.8	0.518
DM	34	66	0.017
Smoke	99.3	97.9	0328
ASA	37.9	49.3	0.652
Beta-blocker	36.9	63.1	0.002
Ejection fractione			
≥ 40%	49.2	50.8	0.797
< 40%	50.8	49.2	
Creatinine			
< 1.5	98.1	75.8	< 0.001
≥ 1.5	1.9	24.2	
Pacing mode			
Atrial based	70.7	57.6	0.022
Ventricular based	29.3	42.4	

*****NT-proBNP means log NT-proBNP. The value of < 300 pg/ml was classified as normal
Chi-square test was used for assessing the association between categorical characteristics and NT-proBNP group

Table 4. Factors associated with high NT-proBNP level by Multiple Logistic Regressions

Independent characteristics	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Ventricular pacing mode	5.74 (2.47, 13.30)	4.86 (2.04, 8.71)	< 0.01
Age (10 years)	2.51 (1.75, 3.59)	1.03 (1.00,1.06)	0.04
creatinine	17.17 (3.18, 92.87)	9.59 (3.81,35.33)	< 0.001

Table 5. Level of log NT-proBNP in different pacing mode

Pacing mode	Mean log NT-proBNP $\pm$ SD	p-value
Atrial based (n = 182)	2.44 $\pm$ 0.67	0.004
Ventricular based (n = 102)	2.67 $\pm$ 0.59	

*****Log NT-proBNP had normal distribution and was used instead of NT-proBNP

> 900 pg/ml, were used in calculation based on suggested cut-off points for diagnosis in acute decompensated heart failure situation[9]. This finding could be explained by ventricular dyssynchrony induced by ventricular pacing which was demonstrated in several previous studies[10-12]. There was the information from studies showing the prognostic value of NT-proBNP in other cardiovascular disease such as congestive heart failure[13,14]. The present study population in the present study included the patients with implanted permanent pacemaker and the prognostic value of NT-proBNP level in this population was uncertain at that time. There were few studies which showed that physiologic, or atrial based pacing resulted in better outcomes compared to ventricular based pacing. The DAVID trial revealed that, in patients with left ventricular systolic dysfunction, a higher percentage of right ventricular pacing was associated with poorer outcomes[15]. Sweeney et al revealed that high ventricular pacing percentage resulted in higher incidence of heart failure and atrial fibrillation[16,17]. With the correlation between high NT-proBNP level and poor outcomes, along with high NT-proBNP level and the ventricular based pacing mode, there is a good support for the conclusion that NT-proBNP could also be used as a prognostic marker in patients with permanent pacemaker.

The terms ventricular based and atrial based may be confusing. As we now understand that right ventricular pacing may be deleterious, knowing the amount of ventricular pacing in the atrial based pacing mode may be another important factor[15,18].

There was information indicating NT-proBNP as the bad prognostic maker for congestive heart failure and acute coronary syndrome[19,20]. However the information from patients with permanent pacemaker is lacking. The impact of pacemaker selection and programming on NT-proBNP level and long term clinical outcomes in this population would be informative and helpful.

The limitations of the present study were: 1) The cross-sectional methodology of this research might result in selection bias. Patients who suffered from heart failure or severe cardiac diseases, which tended to have high NT-proBNP level, were not enrolled. 2) The decision for the pacing mode selection is multifactorial and the tendency for the older and sicker patient to receive the ventricular based pacemaker may be higher than those who were younger with fewer comorbid problems. This confounding factor may not be totally eliminated even with the statistical adjustment. 3) The ventricular pacing percentage, which might affect NT-proBNP level was not recorded and studied. However with atrial based pacing mode, the pacing parameters were previously programmed in order to minimize the ventricular pacing. 4) The nature of underlying bradyarrhythmia was not reported. Patients with atrioventricular block would have higher pacing percentage compared to patients with sinus node dysfunction. 5) A high percentage of patients denied participation in the present study. 6) Left ventricular diastolic function, which could affect NT-proBNP level, was not assessed.

Conclusion

In the patient with permanent pacemaker, four factors are associated with high NT-proBNP level. These are older age, serum creatinine level, left ventricular systolic dysfunction and ventricular based pacemaker.

Potential conflicts of interest

None.

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ความสัมพันธ์ระหว่างระดับ NT-proBNP ในเลือดและวิธีการกระตุ้นหัวใจในผู้ป่วยที่ใส่เครื่องกระตุ้นหัวใจด้วยไฟฟ้าชนิดถาวร

ชาญ ศรีรัตนสถาวร, สัชชนะ พุ่มพฤกษ์, วรางคณา บุญญพิสิฏฐ์, บุรินทร์ ขาวสะอาด, จารุวรรณ คังคะเกตุ

ภูมิหลัง: ระดับ brain natriuretic peptide (BNP) ซึ่งวัดจาก NT-proBNP มีความสัมพันธ์กับภาวะหัวใจล้มเหลว และยังสามารถนำมาใช้บอกพยากรณ์โรคในผู้ป่วยหัวใจล้มเหลวด้วย สำหรับผู้ป่วยที่ได้รับการใส่เครื่องกระตุ้นหัวใจด้วยไฟฟ้าชนิดถาวร มีหลักฐานว่าระดับ BNP สูงขึ้นสัมพันธ์กับอัตราการกระตุ้นหัวใจผ่านเครื่องที่สูง การปรับโปรแกรมเครื่องอาจมีผลต่อระดับ BNP ในผู้ป่วยได้ การศึกษานี้มีเพื่อศึกษาระดับ NT-proBNP ในเลือดผู้ป่วยที่ใส่เครื่องกระตุ้นหัวใจด้วยไฟฟ้าชนิดถาวร และได้รับการโปรแกรมเครื่องแบบต่าง รวมทั้งหาปัจจัย ที่สัมพันธ์กับระดับ NT-proBNP ที่สูงขึ้น

วัสดุและวิธีการ: เป็นการศึกษาแบบ cross-sectional ในผู้ป่วยทุกรายที่มาตรวจติดตามเครื่องกระตุ้นหัวใจด้วยไฟฟ้าที่ศูนย์โรคหัวใจสมเด็จพระบรมราชินีนาถ โรงพยาบาลศิริราช ผู้ป่วยที่ยินยอมเข้าร่วมการศึกษาจะได้รับการตรวจวัดระดับ NT-proBNP ในเลือด และเก็บข้อมูลพื้นฐานจากเวชระเบียนหรือสอบถามจากผู้ป่วย

ผลการศึกษา: ผู้ป่วย 284 รายจาก 402 รายยินดีเข้าร่วมการวิจัย เมื่อแบ่งระดับ NT-proBNP ในเลือดเป็นสามกลุ่มคือ น้อยกว่า 300 พิโคกรัม/มล., 300-900 พิโคกรัม/มล., และมากกว่า 900 พิโคกรัม/มล. พบว่าระดับ NT-proBNP ในเลือดที่สูงมีความสัมพันธ์กับอายุ ระดับครีอะตินีนในเลือด และโปรแกรมการกระตุ้นหัวใจแบบกระตุ้นห้องล่าง โดยมี OR (95% CI) 1.03 (1.00,1.06), 9.59 (3.81,35.33), และ 4.86 (2.04,8.71) ตามลำดับ

สรุป: ปัจจัยที่มีผลทำให้ระดับ NT-proBNP ในเลือดผู้ป่วยที่ใส่เซรื่องกระตุ้นหัวใจด้วยไฟฟ้าชนิดถาวรสูงคือ อายุ ระดับครีอะตินีนในเลือด และ โปรแกรมการกระตุ้นหัวใจแบบกระตุ้นห้องล่าง