Serum N-terminal-pro-Brain Natriuretic Peptide Level and Its Clinical Implications in Patients with Atrial Fibrillation

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ABSTRACT

Background: Brain natriuretic peptide (BNP) is increasingly being used for screening and monitoring of congestive heart failure. However, the role of BNP in patients with atrial fibrillation (AF) and normal left ventricular function has not been determined. This study investigates serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level and its clinical implications in patients with AF.

Methods: Serum NT-proBNP levels were measured by enzyme-linked immunosorbent assay (ELISA) and transthoracic echocardiography was performed in 136 subjects (90 cases with AF and 46 cases with sinus rhythm [SR]). Subjects were excluded if they had a history of myocardial infarction, cardiomyopathy, rheumatic heart disease, or hyperthyroidism that preceded the onset of AF. Controls (n = 30) were from a healthy outpatient primary care population. Potential determinants of serum NT-proBNP levels were identified by univariate and multivariate analyses.

Results: Individuals with AF had higher serum NT-proBNP levels (689.56 ± 251.87 fmol/ml) than those with SR (456.11 ± 148.14 fmol/ml, $P < 0.01$) and control subjects (415.83 ± 62.02 fmol/ml, $P < 0.01$). Individuals with SR and control subjects did not show significant difference at serum NT-proBNP levels ($P > 0.05$). The regression model of serum NT-proBNP levels and clinical predictors showed that presence of AF, older age, and larger right atrial diameter were independently predictive of higher serum NT-proBNP values.

Conclusions: Patients with AF were associated with increased serum NT-proBNP levels. Examining the change of serum NT-proBNP levels is helpful to evaluate the cardiac function in patients with AF.

Introduction

Brain natriuretic peptide (BNP), a cardiac neurohormone predominantly secreted by the heart, is released in responding to the myocyte stretch due to cardiac volume and pressure overload, and therefore regulates the body fluid equilibrium. BNP, a large precursor molecule ($proBNP^{1-108}$), is released from the myocyte, then cleaved by a membrane-bound serine protease (corin) into the inactive N-terminal-$proBNP^{1-76}$ (NT-proBNP) and the smaller active C-terminal 32-amino acid peptide hormone termed $BNP.^{77-108}$ N-terminal-proBNP coexisting in circulation with BNP in 1 to 1 is easy to be determined because of its longer half-life, higher quantity (16-fold to 20-fold higher than BNP), and more stable concentration in the blood. At present, plasma BNP level has an important clinical application in diagnosis, therapy, and prognostication for many cardiac diseases, especially for ventricular dysfunction, acute myocardial infarction (AMI), hypertension, and so forth, but there were few reported studies about BNP in the arrhythmia area. The value of NT-proBNP in atrial fibrillation (AF) has been the least studied. The relationship between serum NT-proBNP levels and AF are discussed in this article.

Methods

Study Subjects

A total of 136 subjects, 95 males and 41 females, with cardiac disease and left ventricular ejection fraction (LVEF) $\geq$50% from the Beijing Hospital between May 2005 and January 2006, were enrolled and divided into 2 groups according to cardiac rhythm (ie, sinus rhythm [SR] or AF). The mean age in the AF group was 71.2 ± 7.9 years, and in the SR group was 69.5 ± 8.8 years. The gender of the subjects between the SR group and AF group was similar. In the AF group, 17 were diagnosed with lone AF (mean age 70.5 ± 8.5 years), 14 males and 3 females. Clinical data were collected by complete review of each patient's medical record, history taking, physical examination, chest x-ray, 12-lead electrocardiogram, and transthoracic echocardiography. Coronary angiography and thyroid function examinations were performed in selected cases. Exclusion criteria were as follows: (1) myocardial infarction within the most recent 3 months, rheumatic heart disease, cardiomyopathy, valvular disease; (2) renal, hepatic, or pulmonary insufficiency; and/or (3) hyperthyroidism. A total of 30 control subjects (mean age 64.0 ± 6.0 years) were selected from a healthy outpatient primary care population from Beijing Hospital during the

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same time. Baseline clinical characteristics of each group is presented in Table 1.

Blood samples were harvested from each subject at enrollment, and a 3-ml blood sample was taken from the antecubital vein after 10 minutes of supine rest in the morning. After 15 minutes of centrifuging with 3000 rpm the serum was extracted, aliquoted, and stored at −70 °Celcius until analysis. The NT-proBNP level was tested by the enzyme-linked immunosorbent assay (ELISA) method using NT-proBNP assay kits (Biomedica Medizinpordukte GmbH & Co KG, Wein, Austria). Assays were performed in a single run and normalized to a standard curve. Interassay coefficients of variation for NT-proBNP was <9%.

Statistical Analysis

All statistical analyses were performed in SPSS 12.0 (SPSS, Inc., Chicago, IL). Data are expressed as mean, ± SD. Differences between each group were assessed using χ^2

Table 1. Baseline Clinical Characteristics of Subjects with AF, SR, and Controls

	the Patients			
Variable	AF Group (n = 90)	SR Group (n = 46)	Controls (n = 30)	*P* Value
Demographics				
Age(y)	71 ± 8[a]	69 ± 9[a]	64 ± 6	<0.01
Sex(male/female)	62/28	33/13	17/13	>0.05
Underlying diseases				
Hypertension	53 (58.89)	30 (65.22)	—	>0.05
Coronary artery disease	20 (22.22)	16 (34.78)	—	>0.05
NYHA functional class				
I	79 (87.78)	40 (86.96)	—	>0.05
II	11 (12.22)	6 (13.04)	—	>0.05
Medications				
β-Blockers	38 (42.22)	28 (60.87)	—	>0.05
ACEI	26 (28.89)	16 (34.78)	—	>0.05
ARB	7 (7.78)	4 (8.70)	—	>0.05
Calcium antagonists	27 (30.00)	16 (34.78)	—	>0.05
Digoxin	5 (5.56)	1 (2.18)	—	>0.05
Aspirin	42 (46.67)	24 (52.17)	—	>0.05
Thiazide diuretics	24 (26.67)	11 (23.91)	—	>0.05
Clinical data				
Heart rate (mean beats/min)	86 ± 25[b]	69 ± 9	73 ± 18	>0.01
LAD (mm)	44 ± 9[b]	36 ± 5	34 ± 6	>0.01
LVEDD (mm)	45 ± 5	44 ± 4	46 ± 3	>0.05
RAD (mm)	39 ± 13[b]	21 ± 5	20 ± 1	>0.01
LVEF	0.64 ± 0.07[b]	0.69 ± 0.07	0.68 ± 0.06	>0.01

Data are presented as the number (percentage) or mean value± SD. [a]P<0.01 (comparsion between patients with AF, SR, and the control group). [b]*P*<0.01 (comparsion between the patients with AF and SR). Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor block; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NHYA, New York Heart Association; RAD, right atrial dimension; SR, sinus rhythm.

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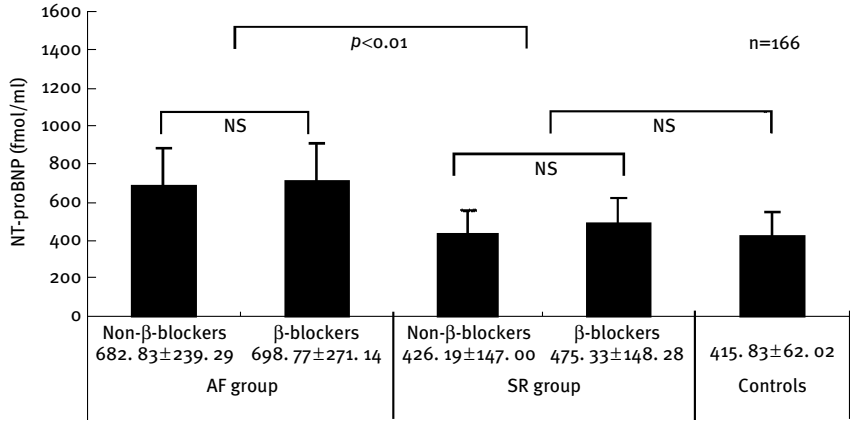

Figure Comparsion of NT-proBNP levels in patients with AF and SR, comparsion of NT-proBNP levels in patients with SR and controls, and comparsion of NT-proBNP levels in patients with and without β-blockers in AF and SR groups, respectively. Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor block; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NHYA, New York Heart Association; RAD, right atrial dimension; SR, sinus rhythm.

statistics for categorical variables and a Student *t* test for continuous variables. Potential determinants of the NT-proBNP levels were identified by univariate analyses, and all identified univariate predictors were then entered in a stepwise manner into a multivariate liner regression model. Statistical significance was defined as $P<0.05$.

Results

There were no significant differences in the baseline diseases between the patients with AF and those with SR. Patients with AF and SR were older than those in the control group, but there was no significant difference in age between AF and SR patients. Patients with AF were found to have higher baseline heart rates, larger diameters of left and right atrium, and lower LVEF than those in the SR group. However, patients with SR were more often prescribed β-blockers than patients with AF.

Patients with AF had significantly higher serum NT-proBNP levels (689.56 ± 251.87 fmol/ml) than those with SR (456.11 ± 148.14 fmol/ml, $P<0.01$) and the control subjects (415.83 ± 62.02 fmol/ml, $P< 0.01$). However, patients with SR and the control subjects did not show significant difference at serum NT-proBNP levels ($P>0.05$). Individuals with paroxysmal AF tended to have high serum NT-proBNP levels (731.09 ± 286.31 fmol/ml) compared to those with persistent AF (676.92 ± 241.30 fmol/ml), but there was no statistical significance ($P>0.05$). Although patients with lone AF had lower serum NT-proBNP levels (634.25 ± 232.22 fmol/ml) than those with cardiac diseases associated with AF (702.44 ± 256.01 fmol/ml), no statistically significant difference ($P>0.05$) was found. Furthermore, whether in the AF or the SR group, patients treated with β-blockers had higher serum NT-proBNP levels than those without β-blockers (non-β-blockers), but there was no significant difference ($P> 0.05$; Figure). The final regression model showed that presence of AF, older age, and larger right atrial diameters were independently predictive of higher serum NT-proBNP values (Table 2).

Discussion

Atrial fibrillation is the most common arrhythmia in clinical practice, accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances, and is an independent predictor of mortality.[1] Hemodynamic impairment and thromboembolic events related to AF accompanied with irregular ventricular response and rapid heart rate result in considerable morbidity and mortality. Previous studies have shown that patients with AF have higher mortality than their age-matched and gender-matched control population, even when adjusted for risk factors; however the risk gradient of AF has not been established clinically.[1] Some studies have demonstrated that the serum levels of BNP may predict the following: the recurrence of AF after direct current cardioversion in patients with mild congestive heart failure;[2] the risk of thromboembolism in patients with nonvalvular AF;[3] the risk of AF occurrence after single-chamber ventricular pacemaker implantation in patients with sick sinus

Table 2. Factors Affecting NT-proBNP Levels

Variable	Partial Coefficients (β)	*t* value	*P* Value
Presence of AF	0.247	2.631	0.01
Age (y)	0.301	4.114	<0.001
RAD (mm)	0.306	3.414	0.001

Abbreviations: AF, atrial fibrillation; RAD, right atrial dimension.

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syndrome;[4] and postoperative AF in patients undergoing cardiac surgery.[5] Therefore, the BNP levels are valuable for the risk stratification, prognostication, and guiding therapy in patients with AF.

BNP, predominantly excreted from the ventricular myocyte, possess vasodilation, sodium excretion, decreased aldosterone levels, inhibition of renin-angiotensin-aldosterone system, inhibition of sympathetic nervous activity, and so forth. Ventricular pressure and volume overload are the important stimuli for BNP synthesis and release.[6] The atrium secretory granules have a few quantities of BNP and release NT-proBNP as a response to atrial stretch and volume overload. Inoue et al[7] was possibly the first to demonstrate that the atrium itself might be the dominant site of BNP production in patients with AF and AF was a condition in which BNP was produced in the atrium itself. Asynchronous contraction of atrial myocardium, which could produce a tethering effect of atrial myocardial fibers, may play an important role in stimulating BNP production. Tuinenburg et al[8] demonstrated that persistent AF induced a higher mRNA expression of pro-BNP on the atrial level, which supported the hypothesis that the atrium is the main source of BNP.

However, it is still under debate whether BNP is independently influenced by AF. In Rossi et al's study,[9] BNP, unlike atrial natriuretic peptide, was not affected by the presence of AF in patients with lone AF, left ventricular dysfunction, or organic mitral regurgitation. Silvet et al's study[10] showed BNP levels were significantly higher in patients with chronic AF than in patients without AF. Jourdain et al,[11], Ohta et al,[12] and Inoue et al[7] described a significant neurohormonal activation promoted by an increase in plasma BNP levels in patients with lone AF. Ellinor et al's study[13] showed NT-proBNP levels were significantly higher in patients with lone AF than in control subjects. The present study evaluated AF patients with normal left ventricular function with or without heart disease, and demonstrated that the presence of AF affects NT-proBNP secretion.

The results showed that NT-proBNP levels were elevated in AF patients with normal left ventricular function with or without heart disease. Although the mean serum NT-proBNP level in the paroxysmal AF group was higher than that in the persistent AF group, no statistically significant difference was found, which agreed with the results of Wozakowska-Kaplan[14] NT-proBNP elevation caused by paroxysmal AF attack resulted from atrial overload (elevation of atrial pressure, stretch of atrial wall, etc) and lack of atrial contribution to left ventricular filling. Furthermore, in patients with persistent AF, the higher levels of NT-proBNP may also be associated with impairment of cardiac function or with an unfavorable hemodynamic profile and altered left ventricular filling pattern resulting from the loss of atrial contraction. This study also showed that the serum NT-proBNP levels in the patients with lone AF were lower than that in the patients with AF and cardiac diseases, and serum NT-proBNP levels in the SR group were higher than that in the control group, but there were no significant differences, which could be due to patients having mild cardiac diseases causing significant elevation of serum NT-proBNP levels.

This study also demonstrated that serum NT-proBNP levels were higher in patients treated with β-blockers than in those without β-blocker therapy, but there was no statistical significance. However, several studies had described that plasma BNP levels were significantly elevated in patients treated with β-blockers and there was a strong independent association between BNP levels and treatment with β-blockers.[10,15,16] The mechanisms of these findings remain unclear, nevertheless, these observations may suggest an important contribution of the cardiac natriuretic peptide system to the therapeutic mechanism of β-blockers, as a result of the effects on BNP secretion and clearance.[15,16]

This article showed that the presence of AF, older age, and greater right atrial dimensions were independent predictors of higher serum NT-proBNP values. Wallen et al's study[17] demonstrated that plasma concentrations of BNP were significantly increased in relation to ageing ($P<.001$) and measurements of BNP may provide prognostic information in the elderly.

It has to be mentioned that diagnosis of heart failure and the evaluation of cardiac function using NT-proBNP in patients with AF require careful consideration, those factors associated with increased NT-proBNP levels, such as AF itself or the use of β-blockers, and so forth, have to be excluded. Regardless of any paroxysmal AF or persistent AF, NT-proBNP during AF is the sum of the BNP released from the ventricle (reflecting left ventricular function) and the atrium (due to AF).

Conclusively, serum NT-proBNP levels are related to the presence of AF and have important clinical values in the diagnosis of heart failure and the evaluation of cardiac function in patients with AF. Nevertheless, this study has its limitations due to the small number of cases, and further research in this area is needed to confirm our findings in a larger population of patients with AF. Meanwhile, the mechanisms increasing NT-proBNP secretion in the myocardium remain unclear and need to be investigated. NT-proBNP, as a biochemical criterion, is measured easily, reliably, and repetitively, but its acute threshold and application in the clinic need large-scale and multicenter clinical studies to be ascertained.

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