Plasma Brain Natriuretic Peptide Levels Indicating Thromboembolism in Very Elderly Patients With Non-Valvular Atrial Fibrillation

Daisuke Watanabe, MD; Kazuhiko Shizuka, MD; Shunichi Koyama, MD; Toshihiko Iwamoto, MD

Background  Assessment of left atrial (LA) function by transesophageal echocardiography is useful for detecting patients with a high risk thromboembolism secondary to atrial fibrillation (AF). A recent study showed that the atrium is the main source of brain natriuretic peptide (BNP) in AF patients without overt heart failure. The purpose of this study was to assess the possible relationship between LA function and plasma BNP levels in very elderly patients with non-valvular AF.

Methods and Results  Seventy-four consecutive patients with chronic non-valvular AF (aged, 82±6 years) underwent transthoracic and transesophageal echocardiography and measurement of plasma BNP. Thirteen AF patients who had a history of cerebral embolism or echocardiographic evidence of thrombus (TE+ group) were compared with 61 AF patients who had no such complications (TE− group). The TE+ group demonstrated a lower LA appendage (LAA) velocity and higher plasma BNP level than the TE− group. Assessment of variables by multiple logistic regression analysis revealed that BNP was a significant predictor of thromboembolism. There was a significant negative correlation between the plasma BNP level and the LAA peak flow velocity.

Conclusions  The present findings would suggest the usefulness of measuring plasma BNP to detect very elderly non-valvular AF patients at high risk for thromboembolism. (Circ J 2007; 71: 1446–1451)

Key Words:  Atrial fibrillation; Brain natriuretic peptide; Thromboembolism; Transesophageal echocardiography; Very elderly patients

Atrial fibrillation (AF) is a sustained arrhythmia that is most commonly found among persons in their 60s, and its incidence is reported to be 2–4% of this generation. In people >75 years old, the incidence of AF has been reported to increase to 11.6%.1–3 Thromboembolism is an important complication of AF that causes deterioration in the quality of life,4,5 but the most appropriate candidates for anticoagulant therapy among patients with AF remain a matter of debate.

Transesophageal echocardiography (TEE) is a useful clinical tool for identifying actual thrombi and for visualizing spontaneous echo contrast (SEC), a change which might predispose patients to develop atrial thrombosis.6–12 The left atrial appendage (LAA) flow velocity measured by TEE has been used as a parameter of LAA function.6,7,12,13 Several investigators have reported that AF patients with a low LAA blood flow velocity (reflecting impaired left atrial (LA) function) have a higher risk of thromboembolism than patients with an appendage flow >20 cm/s.8,12–16 In addition, the thrombin level is increased and platelet activation occurs in patients with either valvular or non-valvular AF.17,18 Abnormal values of these markers might not appear however, until thrombin activation has commenced, and more importantly, such abnormal values might not necessarily reflect changes of cardiac origin.

The level of brain natriuretic polypeptide (BNP) is increased in patients with various heart diseases, such as congestive heart failure,19,20 dilated cardiomyopathy,21 hypertrophic cardiomyopathy,22 hypertensive heart disease,23,24 and lone AF.23,24 Contrary to earlier theories that BNP is mainly secreted by the ventricular myocardium,21,22,23,24 it was reported recently that the left atrium (not the left ventricle) is the main source of BNP in patients with AF.23 The major findings of that study were: (1) patients with AF have significantly higher plasma BNP levels than control subjects; (2) a significant increase of BNP occurs between the coronary sinus (reflecting ventricular secretion) and the anterior interventricular vein (reflecting atrial secretion); and (3) there is a significant decrease of both plasma BNP and atrial BNP production after cardioversion of AF to sinus rhythm.23,24 In the present study, we examined whether plasma BNP levels are higher in very elderly patients with clinical evidence of thromboembolism than in very elderly patients without this complication, and whether plasma BNP levels are correlated with LA function as represented by LAA flow.

Methods  

Patients  We studied 74 patients (38 men and 36 women aged, 75–96 years; mean, 82 years) with ECG-documented AF who were referred to our department for examination of cerebral vascular diseases. All patients underwent transthoracic and TEE, and then were classified into 2 groups.
Patients with a history of cerebral embolism and patients with echographically documented LAA thrombus were classified into the TE+ group, while patients without atrial thrombus or cerebral embolism made up the TE– group. Cerebral embolism was clinically diagnosed according to criteria proposed by Yamaguchi. Non-valvular AF was defined as slowly swirling, smoke-like echos within the left atrium. Gain was continuously adjusted to ensure good visualization and to avoid noise artifacts. The consensus of 2 experienced echocardiographers (DW and KS) was used to define the presence or absence of thrombi and SEC. All TEE studies were performed within 24 h of blood sampling. A transthoracic echocardiographic examination was performed in all patients at the same time as the TEE in the left lateral decubitus position during single-lead ECG monitoring with a 3.75-MHz transducer. The LA and left ventricular (LV) end-diastolic and end-systolic dimensions were derived from 2-dimensional, directed M-mode echocardiography obtained in the parasternal short-axis view.

**Echocardiography**

The TEE studies were performed with a commercially available device (GE Yokogawa Medical System LOGIC 500PRO Version 6.0) equipped with a P509 multiplane transducer. After local anesthesia was provided with 5 ml of 2% xylocaine, the TEE probe was introduced. LAA velocity profiles were obtained by pulsed Doppler echocardiography, with the sample volume set at 1 cm inside the orifice of the LAA. The LAA peak emptying velocity was measured and averaged over 20 consecutive cardiac cycles. LAA flow signals during early diastole correspond to early transmural flow and were not measured when assessing the peak LAA flow velocity. B-mode multiplane echocardiograms and Doppler signals were recorded on videotape for analysis. Thrombi were defined as highly echogenic masses adjacent to the endocardial surface and were clearly differentiated from normal structures such as the pectinate muscles. SEC was defined as slowly swirling, smoke-like echoes within the left atrium. Gain was continuously adjusted to ensure good visualization and to avoid noise artifacts. The consensus of 2 experienced echocardiographers (DW and KS) was used to define the presence or absence of thrombi and SEC. All TEE studies were performed within 24 h of blood sampling. A transthoracic echocardiographic examination was performed in all patients at the same time as the TEE in the left lateral decubitus position during single-lead ECG monitoring with a 3.75-MHz transducer. The LA and left ventricular (LV) end-diastolic and end-systolic dimensions were derived from 2-dimensional, directed M-mode echocardiography obtained in the parasternal short-axis view.

**Blood Sampling and Assays**

Blood sampling and plasma natriuretic peptide measurements were performed as reported previously. Briefly, samples were obtained within a 24-h period before TEE after the patient had rested. Blood samples were collected from a peripheral vein into tubes containing aprotinin and EDTA, and the plasma was separated and stored at –80°C until analysis. The plasma BNP and atrial natriuretic peptide (ANP) concentrations were measured with immunoradiometric assays by using a commercial kit for BNP (MI 02, Shionogi Co Ltd, Osaka, Japan) and a kit for ANP.
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Windows; SPSS Japan Co, Tokyo, Japan).

calculated to compare the prognostic value of each variable.

odds ratios (ORs) and 95% confidence intervals were cal-

peak flow velocity, SEC, ANP, BNP, and D-dimer. The

predict an embolic event, with the variables tested being the

was performed to test whether any of the parameters could

LAA flow velocity. Multiple logistic regression analysis

systolic blood pressure (BP), diastolic BP, D-dimer, and

tations were measured with a latex photometric immunoassay

with trisodium citrate. Then, plasma D-dimer concentra-

measurement of D-dimer were subjected to anticoagulation

(Shionoria, Shionogi Co Ltd). Venous blood samples for the

measurement of D-dimer levels and ANP levels. (Solid dot) Patients with a history of cerebral embol-

ism or left atrial appendage (LAA) thrombus (TE+ group); (Hollow dot) patients without complications (TE– group).

Statistical Analysis

Comparison of echocardiographic and hemodynamic parameters between the 2 groups was performed using non-

parametric analysis with the Mann-Whitney U-test. The frequency of SEC was compared with a 2×2 $\chi^2$ test. Linear

regression analysis was used to examine the relationship be-

between plasma BNP/ANP levels and the age, ventricular rate,

systolic BP, diastolic BP, LAA peak flow velocity. Multiple logistic regression analysis was performed to test whether any of the parameters could predict an embolic event, with the variables tested being the age, gender, ventricular rate, systolic and diastolic BP, LAA peak flow velocity, SEC, ANP, and D-dimer. The odds ratios (ORs) and 95% confidence intervals were calculated to compare the prognostic value of each variable. All analyses were performed with the Statistical Package for the Social Sciences software (version 11.0 J for Windows; SPSS Japan Co, Tokyo, Japan).

Results

Clinical Characteristics

The clinical parameters of the patients are shown in Table 1. In the TE– group, 6 patients without cerebral embolism had thrombi in the LAA that were identified by TEE and the other 7 patients had a history of cerebral embolism (affecting the internal carotid system in 2 patients and the vertebrobasilar system in 5 patients). There were significant differences between the 2 groups with regard to systolic and diastolic BP. There were no significant differences between the 2 groups with respect to age, gender, hyperlipidemia, diabetes mellitus, transthoracic echocardiographic parameters, ventricular rate, D-dimer, ANP, and drug therapy.

Table 2 Results of Multivariate Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Continuous variables</th>
<th>p value</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.844</td>
<td>1.012 (0.896–1.144)</td>
</tr>
<tr>
<td>Gender</td>
<td>0.829</td>
<td>0.857 (0.721–2.473)</td>
</tr>
<tr>
<td>Ventricular rate</td>
<td>0.698</td>
<td>1.018 (0.930–1.144)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.016</td>
<td>1.152 (1.027–1.292)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.04</td>
<td>1.125 (1.005–1.258)</td>
</tr>
<tr>
<td>LAA peak flow velocity</td>
<td>0.062</td>
<td>0.939 (0.878–1.003)</td>
</tr>
<tr>
<td>SEC</td>
<td>0.016</td>
<td>6.750 (1.426–31.895)</td>
</tr>
<tr>
<td>ANP</td>
<td>0.052</td>
<td>1.009 (1.001–1.016)</td>
</tr>
<tr>
<td>BNP</td>
<td>0.019</td>
<td>1.022 (1.004–1.040)</td>
</tr>
<tr>
<td>D-dimer</td>
<td>0.282</td>
<td>1.269 (0.823–1.957)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval. Other abbreviations are as shown in Table 1.

Table 3 Correlations With BNP and ANP

<table>
<thead>
<tr>
<th></th>
<th>BNP</th>
<th>ANP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>p value</td>
<td>CC</td>
</tr>
<tr>
<td>Age</td>
<td>0.207</td>
<td>0.247</td>
</tr>
<tr>
<td>Ventricular rate</td>
<td>0.003</td>
<td>0.986</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.349</td>
<td>0.047</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.353</td>
<td>0.044</td>
</tr>
<tr>
<td>D-dimer</td>
<td>0.58</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CC, correlation coefficient. Other abbreviations are as shown in Table 1.

Transthesophageal Echocardiographic Findings

The LAA peak flow velocity was significantly lower in the TE+ group than in the TE– group and SEC was more common in TE+ group than in the TE– group.

Plasma ANP and BNP Levels

The mean plasma ANP level for all 74 patients was 118.8±80.8 pg/ml (range; 17–410 pg/ml), while the mean plasma BNP level was 288.4±235.6 pg/ml (range; 16.6–1,250 pg/ml). There was a significant difference of plasma ANP and BNP levels between the TE+ and TE– groups (Table 1). There was no significant correlation between the plasma BNP levels and ANP levels (Fig 1).

Factors Predicting Cerebral Embolism (Multiple Logistic Regression Analysis)

The results of regression analysis are shown in Table 2. Systolic and diastolic BP, SEC, and BNP were independent predictors of cerebral embolism (OR, 1.152, p=0.016; OR, 1.125, p=0.040; OR, 6.750, p=0.016; OR, 1.022, p=0.019, respectively).

Correlations With Plasma BNP or ANP Levels

Table 3 shows the correlation of each factor with the BNP and ANP levels. Fig 2 shows the relationship between plasma BNP and the LAA peak flow velocity. The plasma BNP level showed a significant negative correlation with LAA peak flow velocity (r=–0.436, p=0.015), but no significant correlation was found between the plasma ANP level and LAA peak flow velocity. Plasma BNP also showed a significant positive correlation with D-dimer (r=0.580, p=0.001), but no significant correlation was found between the plasma ANP and D-dimer levels. Furthermore, plasma BNP showed a weak, but significant, positive correlation with the systolic BP and diastolic BP (r=0.349, p=0.047 and r=0.353, p=0.044, respectively), but no significant correlation was found between plasma ANP and BP.
Discussion

The present study demonstrated that: (1) the plasma BNP level is higher in very elderly patients with a history of cerebral embolism than in those without it; (2) there is a significant negative correlation between the plasma BNP level and the LAA peak flow velocity, as well as a significant positive correlation between plasma BNP and D-dimer; and (3) BNP is an independent predictor of cerebral embolism in very elderly patients with non-valvular AF. Plasma BNP has closely related not only to LAA flow velocity, which directly reflect LAA function, but also to D-dimer, which is suggested to be the hypercoagulated state in vessels. Patients with LAA dysfunction and who were in a hypercoagulated state have been reported to be at high risk of CE. The present study suggested that plasma BNP might be a useful marker to detect patients at a high risk of CE.

It is widely known that BNP is secreted from the ventricle and that elevated BNP levels are correlated with LV systolic and diastolic dysfunction. In addition, previous studies have shown that the BNP level is correlated with the LV filling pressure. In the present study, the BNP level was higher in the TE+ group than in the TE− group, but the BNP level in the TE− group was still higher compared with the normal population. The precise mechanism of high BNP level is not to be clarified, however, LV diastolic dysfunction might lead to more secretion of BNP. It has recently been reported that elevation of the plasma BNP level in patients with chronic AF is caused by an increase of BNP secretion from the atria. Secretion of BNP from the atria might be the cause of different BNP levels between the 2 groups.

In the present study, there was a significant correlation between the plasma BNP level and the LAA peak flow velocity. None of our patients with AF had overt heart failure. There were no significant differences between the 2 groups in terms of the serum creatinine level and transthoracic echocardiographic parameters, which indicates that plasma BNP levels were not influenced by renal function or conventional cardiac function. Previous studies have pointed out that atrial pressure overload leads to the elevation of the plasma BNP level in patients with pure mitral stenosis.

Inoue et al and Ohta et al have consistently demonstrated a significant reduction of the plasma BNP level and a decrease in the difference of BNP between the anterior interventricular vein (reflecting atrial secretion) and the coronary sinus (reflecting ventricular secretion) in patients with AF after cardioversion. Significantly, atrial BNP production did not return to the normal range after cardioversion. Thus, other factors might also influence the plasma BNP level.

Frustaci et al reported that atrial biopsy specimens from patients with lone AF demonstrated a variety of changes such as severe hypertrophy, fibrosis, and inflammation. Saito et al reported that the tissue of the LAA in patients with valvular AF showed significantly greater hypertrophy of cardiomyocytes, nuclear enlargement, bizarre nuclei, intercellular fibrosis, and endocardial thickening. All of these pathological changes are well known to enhance BNP production in the ventricular myocardium. Thus, it is possible that pathological changes of the atrial myocardium might underly the increase of BNP secretion in very elderly patients with poor LA function.

Previous studies have also demonstrated that, compared with persons in sinus rhythm, thrombogenic and fibrinolytic markers are increased in patients with AF, indicating the existence of a prothrombotic state. In the present study, a significant positive correlation was found between plasma D-dimer and BNP levels. Therefore, we suggest that a high plasma BNP level might indicate a hypercoagulated state in very elderly patients who have non-valvular AF without overt heart failure.

In the present study, plasma BNP measurement was demonstrated to be useful for predicting the risk of thromboembolism. Effective prevention of thromboembolic complications by medications, including aspirin and warfarin, might have masked the actual vulnerability to thromboembolism of the patients enrolled in the present study. However, cerebral embolism occurred in 1 patient from the TE+ group after evaluation by TEE and measurement of BNP. This patient had a high plasma BNP level (396 pg/ml) and a low LAA peak flow velocity (13.6 cm/s). Although these data are consistent with the concept that very elderly patients with AF and high plasma BNP levels might be vulnerable.
to thrombosis, a prospective study needs to be performed to confirm this conclusion.

ANP is mainly synthesized in and secreted from the atria, and the plasma ANP level is increased in patients with congestive heart failure. In the present study, there was no correlation between plasma ANP and the LAA peak flow velocity. Plasma ANP levels are higher in patients with congestive heart failure plus AF and Van Den Berg et al recently reported that the plasma ANP level shows an inverse relationship with the duration of AF. In the present study, there were significant differences of systolic and diastolic BP between the TE+ and TE– groups, so we could not exclude the possibility that the significant difference of plasma BNP levels between the 2 groups was partly related to BP. The LV diastolic function was not examined in the present study. However, previous studies reported a close association between plasma BNP level and LV diastolic function. Therefore, higher BNP levels might be due to LV diastolic dysfunction in the TE+ group. Third, some patients in the present study had a higher plasma BNP without having overt heart failure. In very elderly patients, an impaired coronary system might exist subclinically or plasma BNP might be influenced with advancing age itself.

In conclusion, TEE showed that LAA peak flow velocity was lower in very elderly patients with a history of cerebral embolism, and the plasma BNP level was negatively correlated with the LAA flow velocity. Plasma BNP reflects LA function and might be a useful marker of vulnerability to thromboembolism in very elderly AF patients without overt heart failure.

References


