High Plasma Brain Natriuretic Polypeptide Level as a Marker of Risk for Thromboembolism in Patients With Nonvalvular Atrial Fibrillation

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Background and Purpose—Assessment of left atrial appendage (LAA) function with transesophageal echocardiography is useful for detecting patients at high risk for thromboembolism as a result of atrial fibrillation (AF). A recent study reported that the atrium is the main source of brain natriuretic polypeptide (BNP) in AF patients without overt heart failure. The purpose of this study was to assess a possible relationship between LAA function and plasma BNP levels in nonvalvular AF.

Methods—Thirty-four consecutive patients with chronic nonvalvular AF (age, 69±9 years) underwent transesophageal echocardiography and plasma BNP measurement. Thirteen patients with a history of thromboembolism or echocardiographic evidence of thrombus (E+ group) were compared with 21 AF patients without complications (E− group).

Results—The E+ group patients demonstrated greater impairment of LAA velocity and higher plasma BNP levels than the E− group patients (LAA velocity: 12±6 versus 31±17 cm/s, P<0.05; plasma BNP: 126±53 versus 86±45 ng/L, P<0.05). Overall analysis of the continuous variables with multiple logistic regression analysis revealed that BNP was a significant predictor of thromboembolism. There was a weak but significant negative correlation between plasma BNP levels and LAA flow velocity (r=0.38, P<0.05). No intergroup difference in plasma atrial natriuretic polypeptide levels was found.

Conclusions—The present data suggest the usefulness of measuring plasma BNP levels, which may reflect augmented atrial secretion of BNP from the impaired atrial myocardium, in detecting patients at high risk for thromboembolic complications in nonvalvular AF. (Stroke. 2002;33:1005-1010.)

Key Words: atrial fibrillation | natriuretic peptide, brain | thromboembolism

Atrial fibrillation (AF) is a sustained arrhythmia that is commonly found in people in their 60s, and its incidence has been reported to be 2% to 4% of this generation. In people >75 years of age, 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 patient’s quality of life.4,5 Proper selection of candidates for anticoagulation therapy among patients with AF is thus a matter of debate.

Transesophageal echocardiography (TEE) is a useful clinical tool for both identifying actual thrombi and visualizing spontaneous echo contrast (SEC), which may predispose a patient to atrial thrombus formation.6–12 Left atrial appendage (LAA) flow velocity, measured by TEE, has been used as functional parameter of the LAA.6,7,12,13 Several investigators have reported that patients with AF who have a low appendage blood flow velocity, reflecting impaired LAA function, have a higher risk of thromboembolism than patients with an appendage flow >20 cm/s.8,12–16

On the other hand, a biochemical approach to circulating blood enables us to assume thrombin activation and platelet enhancement in patients with either valvular or nonvalvular AF.17,18 Abnormal values for these biochemical markers may not appear, however, until thrombin is actually being activated, and more important, these abnormal values may not necessarily be of cardiac origin.

Brain natriuretic polypeptide (BNP), which increases in patients with heart disease such as congestive heart failure,19,20 dilated cardiomyopathy,21 hypertrophic cardiomyopathy, hypertensive heart disease,22 and lone AF,23,24 has been used as a biochemical parameter produced in the heart. Contrary to earlier theories that BNP is secreted mainly from the ventricular myocardium,21,25,26 it has been reported recently that the left atrium, not the left ventricle, is the main
source of BNP in patients with AF. The major important findings in that study were that patients with AF show (1) significantly higher plasma BNP levels than control subjects; (2) a significant increase in BNP occurring between the coronary sinus and the anterior interventricular vein, reflecting atrial secretion of BNP; and (3) a significant decrease in both plasma BNP levels and atrial BNP production after DC cardioversion of AF to sinus rhythm. However, the question of why a wide variation in plasma BNP levels remains unanswered.

In the present study, we examined the question of whether plasma BNP levels are higher in patients with clinical evidence of thromboembolism than in patients without complications and, if so, whether plasma BNP levels correlate with left atrial function as represented by LAA flow.

**Subjects and Methods**

**Study Patients**

We studied 34 patients (29 men, 5 women; age, 44 to 89 years; mean, 69 years) with ECG-documented AF. We roughly estimated the duration of AF by the longest interval between 2 time points of ECG-confirmed AF. All patients underwent echocardiography via both the transthoracic and the transesophageal approach and were classified into 2 groups. Patients with episodes of sudden onset of organ ischemia confirmed by imaging and patients with echographically documented thrombus in the LAA were classified into the E+ group. Anatomic information regarding occluded arteries was documented by CT/MRI or digital subtraction angiograms performed at the university hospital or other affiliated medical centers. Patients without embolism-related complications made up the E− group. Patients with valve malfunctions were excluded. Nonvalvular AF was defined by the following criteria: absence of mitral stenosis or prosthesis, absence of a history of cardiac surgery, absence of severe mitral regurgitation (grade 3 or greater by color Doppler echocardiography), and absence of evidence of congenital heart disease.

None of the following conditions were present in any of the patients in the present study: medication with diuretics, symptomatic congestive heart failure (New York Heart Association class II or greater), evidence of congenital heart disease or organ failure, or malignancy. Written, informed consent was obtained from all subjects before the study.

**Echocardiographic Study**

All TEE studies were performed with commercially available devices (Agilent Technology SONOS 5500, ATL HDI 5000, Toshiba SSA-380A, Aloka SSD-2200) equipped with 5-MHz phased-array multipane transducers. After local anesthesia with topical lidocaine, the TEE probe was introduced. LAA velocity profiles were obtained by pulsed Doppler echocardiography, with the sample volume placed 1 to 2 cm into the orifice of the LAA (Figures 1 and 2). LAA peak emptying velocities were measured and averaged over 5 consecutive cardiac cycles. LAA flow signals during the early diastolic phases correspond to early transmural flow and were not measured as peak LAA flow velocities. B-mode multipane echocardiograms and Doppler signals were recorded on videotape for analysis. Thrombi were defined as highly echogenic masses adjacent to the endocardial surface and clearly differentiated from such normal structures as pectinate muscles. SEC was defined as slowly swirling, smokelike echoes within the left atrium. SEC was classified as “faint” when localized within the LA or LAA and intermittent or enhanced gain setting was required for detection and as “dense” when it was persistent throughout the LA and LAA. Gain was continuously adjusted to ensure visualization and to avoid noise artifact. The consensus of 2 experienced echocardiographers (H.S., Y.O.) was used to define the presence or absence of thrombi and SEC. TEE studies were performed within 24 hours of blood sampling. Trans-thoracic echocardiographic examination was performed in all patients at the same time as TEE in the left lateral decubitus position during single-lead ECG monitoring with a 3.75-MHz transducer. The left atrial and left ventricular 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 Natriuretic Polypeptide Hormone Assay**

Blood sampling and plasma natriuretic polypeptide hormone measurements were performed as previously reported. Briefly, samples were obtained within the 24-hour period before TEE with the patients on bedrest. Blood samples were collected from a peripheral vein into tubes containing aprotinin and EDTA, and the plasma was stored in an −80°C freezer until analysis. Plasma BNP concentration was measured with an immunoradiometric assay specific for human BNP using commercial kits (Shionoria, Shionogi Co Ltd). Blood sampling for natriuretic peptide measurements was performed before thromboembolic events in 3 of 11 patients (average interval, 6.7 ± 9.8 months; range, 6 days to 18 months) and after events in 8 of 11 patients (average, 17 ± 24 months; range, 3 days to 5 years).

**Cardiac Catheterization**

Eighteen patients with AF underwent cardiac catheterization for evaluation of coronary artery disease because of either chest pain or chest discomfort. Before catheterization, the purpose of the study was explained to each subject, and his or her informed consent was obtained. Catheterization was performed by the transfemoral ap-

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**Figure 1.** B-mode echocardiograms and LAA flow velocity from a representative patient with an embolic event (E+ group). Left, Thrombus in the LAA with SEC; lower right, decreased LAA flow velocity. LAA peak emptying flow velocity was 7 cm/s; plasma BNP concentration was 216.1 ng/L.
Results

Clinical Characteristics

The clinical parameters of the patients are shown in Table 1. Two patients without thromboembolic events had echocardiographically documented thrombi in the LAA that were identified by TEE. Eleven patients had a history of systemic thromboembolic events: cerebral infarction in 7 patients, appendicular artery obstruction in 3 patients, and superior mesenteric artery embolism in 1 patient. The duration of AF ranged from 1 day to 36 years (average, 5.2 years). Figures 1 and 2 show representative B-mode echocardiograms of the LAA and Doppler flow signal recordings from the E+ and E− groups.

Echocardiographic Findings

Peak LAA flow velocity was lower in the E+ group than in the E− group. Dense SEC was present more frequently in E+ than in E− patients. The E+ group showed significantly better fractional shortening than the E− group, but both were within the normal range. The hemodynamic parameters obtained from the 18 patients were also within normal ranges.

Plasma ANP and BNP Levels

The mean plasma ANP level for all 34 patients was 44.9±31.9 ng/L (range, 7.2 to 130.0 ng/L), and the mean plasma BNP level was 101.2±51.5 ng/L (range, 32.0 to 220.0 ng/L). There was a significant difference in plasma BNP levels between the E+ and E− groups (Table 1), but plasma ANP levels did not differ significantly between the groups. In the E+ group, 11 patients had a history of thromboembolic events.

Factors Predicting Thromboembolic Complications With Multiple Logistic Regression Analysis

Results are shown in Table 2. BNP was an independent predictor of thromboembolic complication.

Comparison of Echocardiographic Parameter of LAA Function and Plasma BNP

Plasma BNP levels showed a weak but significant negative correlation with LAA peak velocity (Figure 3, right), but no significant correlation was found between plasma ANP levels and LAA peak velocity (Figure 3, left).

Discussion

The present study demonstrated that (1) plasma BNP levels were higher in patients with episodes of thromboembolism than in patients without complications; (2) LAA peak flow velocity, evaluated by transesophageal Doppler echocardiography, was lower in the E+ group than in the E− group; (3) there was a weak but significant negative correlation between plasma BNP levels and LAA peak flow velocity; and (4) BNP is an independent predictor of thromboembolism.

TEE offers unique diagnostic resolution of the LAA, which is a frequent site of thrombus formation in AF, and this facilitates thrombus detection and measurement of flow velocity. Measurement of the peak velocity of LAA blood outflow by Doppler interrogation during TEE has been proposed as a method of assessing the degree of blood stasis.

Statistical Analysis

Comparison of the echocardiographic and hemodynamic parameters between the 2 groups was performed by nonparametric analysis with the Mann-Whitney U test. SEC frequency was compared with 2×2 χ2 test. Linear regression analysis was performed to examine the relationship between LAA flow velocities and plasma BNP/atrial natriuretic polypeptide (ANP) levels. Multiple logistic regression analysis was performed to test whether each parameter predicts embolic events. Predictor variables tested were age, ventricular response rate, systolic blood pressure, LAA peak velocity, LA dimension, fractional shortening, cardiac mass index, ANP, and BNP. Odds ratios within 95% confidence intervals were shown to compare the prognostic value of each variable. Statistical analysis was performed with the GBSTAT statistical analysis package (version 6.5, Dynamic Microsystems, Inc). A value of P<0.05 was considered statistically significant.
Although the association of thrombus with SEC and impaired LAA velocity may have been weakened in the present study by anticoagulation therapy, 46% of patients in the E+ group demonstrated a thrombus in the LAA. Echocardiographic assessment by multiplane TEE may have helped to demonstrate a higher incidence than that reported in studies using biplane TEE.9,10 Patients with a previous history of thromboembolism in the present study typically demonstrated 2 echocardiographic abnormalities: dense SEC and low LAA flow. At the present time, TEE is one of the most sensitive and reliable methods for selecting patients at relatively high risk of thromboembolism. On the other hand, biochemical markers of intracardiac thrombi are sometimes preferable when TEE is not the best choice for examination, as for patients with pulmonary disease, backbone deformities, or esophageal disease.27 Platelet factor 4, a packed protein inside circulating platelets that is secreted on activation, has been reported to be associated with AF in some patients,28 and markers of thrombin activity such as thrombin–antithrombin III complex, D-dimer, and prothrombin fragment I have also been reported in patients with AF.17,18,29,30 These biochemical parameters, however, may not be in the abnormal range until thrombi formation is actually taking place, and more important, they are not necessarily of cardiac origin.

In the present study, plasma BNP measurement was demonstrated to be useful for prediction of thromboembolism. Effective prevention of thromboembolic complications by medication, including aspirin, warfarin, or both, may have masked real vulnerability to thromboembolism in the patients enrolled in the present study. However, thromboembolic events occurred in 2 patients in our E+ group after their evaluation by TEE and BNP measurement. Both of these patients had very high plasma BNP levels (216.1 and 160.0 ng/L) and very low LAA flow velocities (7 cm/s for both). One of the patients experienced a thromboembolism while receiving insufficient warfarin (international normalized ratio >1.5) and the other when warfarin was discontinued before minor surgery. Although these data are consistently suggesting that patients with high plasma BNP levels may be vulnerable to thrombus formation, further prospective study needs to be performed.

It has recently been reported that elevation of plasma BNP levels in patients with chronic AF is due to augmentation by BNP secreted from the atrium.23,24 In that study, the authors performed cardiac catheterization and confirmed that

<table>
<thead>
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<th>Continuous Variables</th>
<th>P</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Age</td>
<td>0.057</td>
<td>1.386 (0.992–1.937)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.376</td>
<td>0.235 (0.010–5.784)</td>
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<tr>
<td>Current smoking</td>
<td>0.638</td>
<td>2.719 (0.033–223.8)</td>
</tr>
<tr>
<td>Ventricular response rate</td>
<td>0.490</td>
<td>0.944 (0.834–1.067)</td>
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<tr>
<td>Systolic BP</td>
<td>0.062</td>
<td>0.944 (0.834–1.067)</td>
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<tr>
<td>LAA peak flow velocity</td>
<td>0.217</td>
<td>0.795 (0.553–1.144)</td>
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<tr>
<td>LA dimension</td>
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<td>1.109 (0.880–1.397)</td>
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<td>FS</td>
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<tr>
<td>LV mass index</td>
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<td>1.002 (0.959–1.046)</td>
</tr>
<tr>
<td>ANP</td>
<td>0.053</td>
<td>0.929 (0.853–1.001)</td>
</tr>
<tr>
<td>BNP</td>
<td>0.032</td>
<td>1.073 (1.006–1.144)</td>
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Abbreviations as in Table 1, plus OR indicates odds ratio; CI, confidence interval.

![Image](http://stroke.ahajournals.org/Downloadedfrom)

**TABLE 2. Results of Multivariate Logistic Regression Analysis**

**Figure 2.** Representative patient with no embolic event (E− group). Left, Horizontal view of the LAA. LAA peak emptying velocity was 33 cm/s; plasma BNP concentration was 41.4 ng/L.

**Figure 3.** Right, Relationship between plasma BNP level and LAA peak flow velocity. Plasma BNP levels shows a weak but significant negative correlation with LAA peak flow velocities. Left, Relationship between plasma ANP level and LAA peak flow velocity. No significant correlation was found. • indicates patients with a history of systemic thromboembolic events or left atrial thrombus (E+ group); ○; patients without thromboembolic events (E− group).
In the present study, there was a weak but significant correlation between plasma BNP levels and LAA velocity. None of the patients with AF had overt heart failure. LV function is demonstrated by fractional shortening (Table 1). Factors regulating atrial production of BNP thus need to be discussed. Previous studies have pointed out that atrial pressure overloading leads to an elevation of plasma BNP levels in patients with pure mitral stenosis. However, the pulmonary artery wedge pressure values for the 2 groups in our study were not significantly different, and no significant mitral valve disease was present in our patients. Inoue et al and Ohta et al consistently demonstrated that a significant reduction in plasma BNP levels and in the difference in BNP concentration between the anterior interventricular vein and the coronary sinus occurred after DC cardioversion in patients with AF. Significantly, atrium-derived BNP after cardioversion did not return to the normal range. Thus, other factors may also contribute to plasma BNP levels.

Atrial enlargement is a well-known change that occurs in the atria of patients with AF. Microscopic changes such as fibrosis or lipid degeneration have been reported in pathological examination of hearts with organic heart disease. 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. All these pathological changes are well-known causes of enhanced production of BNP in the ventricular myocardium. It is thus possible that pathological changes in the atrial myocardium may also be underlying factors in elevated BNP secretion in patients with poor LAA function.

In conclusion, plasma BNP levels were higher in patients with thromboembolic complications than in patients without complications. TEE evaluation showed that LAA flow was also more severely impaired in the patients with a history of thromboembolic complications, and plasma BNP levels correlated negatively with LAA flow velocity. Plasma BNP as a reflection of LAA function may be a useful marker to predict vulnerability to thromboembolism in AF patients without overt heart failure.

References


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