Original Article

Elevated Plasma Brain Natriuretic Peptide Levels Independent of Heart Disease in Acute Ischemic Stroke: Correlation with Stroke Severity

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We tested the hypothesis that plasma brain natriuretic peptide (BNP) levels are elevated in patients with acute cerebrovascular diseases (CVD) independent of heart disease, and reflect CVD severity. After careful evaluations for heart disease, the study included 79 consecutive patients with CVD without any evidence of heart disease admitted within 48 h after onset (71±10 years), and 26 control subjects without CVD (CT, 67±12 years). Ischemic stroke subtypes were defined by the TOAST classification. Large-artery atherosclerosis (LAA, n=27), small-artery occlusion (SAO, n=27), and intracerebral hemorrhage (ICH, n=25) were included. The plasma BNP levels were measured at admission and 1 month later. Stroke severity and brain infarct volume were evaluated. There were no significant differences in the clinical profiles including echocardiographic parameters among the groups. The plasma BNP level (pg/mL) upon admission was higher in LAA (70.6±53.9) than in SAO (38.2±28.4) and CT (28.5±19.9) (both p<0.05). The level in ICH (47.3±28.6) was not significantly different from that in CT. The BNP level in ischemic stroke was positively correlated with the NIH Stroke Scale (NIHSS) (ρ=0.42, p<0.05) and infarct volume (r=0.34, p<0.05). Brain infarct volume and NIHSS were independent contributors to the plasma BNP level in ischemic stroke. One month later, the BNP level was significantly decreased and was similar in all CVD groups. The plasma BNP level transiently increased in patients with LAA independently of heart disease, and reflected infarct volume and the severity of acute ischemic stroke. (*Hypertens Res* 2008; 31: 1695–1702)

***Key Words*: natriuretic peptides, stroke, acute ischemic, heart diseases**

Introduction

Brain natriuretic peptide (BNP) is released mainly from the left ventricle in response to volume expansion and pressure overload. Plasma BNP levels, therefore, are elevated in patients with left ventricular dysfunction and are recognized as a useful biochemical marker for evaluating the severity of congestive heart failure (CHF) (*1*–*3*). BNP was originally isolated from the porcine brain (*4*), and has also been detected in the rat brain where its expression is upregulated by middle cerebral artery occlusion (*5*, *6*). There are, however, only limited data on its physiological and pathological roles in the human brain.

Recent studies have shown that BNP or N-terminal pro-BNP (NT-proBNP), a circulating precursor of BNP, is ele-

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vated in patients with acute ischemic stroke (*7–10*). Those studies, however, may include the patients with various heart diseases such as CHF, myocardial infarction, cardiomyopathy, hypertensive heart diseases, valve diseases, and paroxysmal or chronic atrial fibrillation, which significantly influence the plasma levels of BNP (*2*, *11–15*). In this study, we carefully evaluated whether any heart diseases were present or not in patients with acute cerebrovascular disease (CVD) admitted within 48 h after onset. After exclusion of those patients with such heart diseases, we investigated whether the plasma BNP levels were elevated in patients with CVD independently of heart disease. We further investigated whether the plasma BNP level reflected the severity of CVD.

Methods

Study Patients

From October 2005 to February 2006, 172 consecutive patients with acute CVD were admitted to Hirosaki Stroke Center within 48 h after symptom onset. All patients underwent computed tomography of the brain. If intracerebral hemorrhage was not detected, we further performed MRI including transversal diffusion weighted image (DWI), T_2-weighted image, fluid-attenuated inversion recovery (FLAIR) and MR angiography (Signa EXCITE HD 1.5T; GE Medical Systems, Waukesha, USA), and carotid ultrasonography. To evaluate the underlying or preexisting heart diseases, all patients underwent standard 12-lead ECG, monitoring of ECG in the stroke care unit, Holter 24-h ECG during the subacute stage, chest X-ray, and transthoracic echocardiography. Transesophageal echocardiography was also performed to detect thrombus in the left atrial appendage and the patent foramen ovale as a cardioembolic source in patients with cardioembolic (CE) infarction. Based on these examinations, 71 patients were excluded because of CHF (n=2), previous myocardial infarction (n=2), cardiomyopathy (n=3), valvular diseases (n=10), and chronic or paroxysmal atrial fibrillation (n=54). In addition, we excluded 19 patients with subarachnoid hemorrhage (n=4), renal dysfunction (creatinine >1.1 mg/dL) (n=12), and malignant diseases (n=3). Control subjects (CT, n=26, 67±12 years), who visited the emergency room and were not diagnosed as having CVD were also enrolled (epilepsy [n=3], vertigo [n=10], headache [n=5], paresthesia [n=2], infectious disease [n=2], anemia [n=1], hypoglycemia [n=1], neurally mediated syncope [n=2]). These control subjects did not have any type of heart disease. The protocols and the process for obtaining informed consent were approved by the Institutional Review Board.

Stroke Classification

CVD patients were classified as either ischemic stroke or intracerebral hemorrhage (ICH). Ischemic stroke patients were further classified into large-artery atherosclerosis (LAA), small-artery occlusion (SAO), CE infarction, other determined causes, and undetermined causes, according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (*16*). LAA (n=27, 74±8 years) was defined as cortical or subcortical infarct with either significant (>50%) stenosis or occlusion of a major brain artery or a branch cortical artery corresponding to neurological deficits and without any evidence of a cardiac source of emboli. Patients with at least one traditional clinical lacunar syndrome and no evidence of cerebral cortical dysfunction, with brain imaging findings of a relevant brain stem or subcortical hemispheric lesion with a diameter of less than 1.5 cm, and without any evidence of a cardiac source of emboli were included in SAO group (n=27, 70±8 years). CE infarction, which was defined as sudden onset of symptoms, presence of potential cardiac sources of emboli, multiple brain infarcts involving multiple arterial territories, and the absence of either significant stenosis or occlusion in the ipsilateral artery, was excluded. This was based on the finding that most of the patients with CE infarction had chronic or paroxysmal atrial fibrillation, which extremely influences the plasma BNP levels (*14*). We did not detect the patent foramen ovale in patients with CE infarction. Patients with other determined or undetermined causes without any heart diseases were also excluded because of small sample sizes. ICH (n=25, 68±13 years) was diagnosed when intracerebral hemorrhage was recognized on computed tomography. In the patients with ischemic stroke, brain infarct volume was measured by analyzing DWI using specific 3D software (ZIOSTATION Ver.1.0; AMIN Inc., Tokyo, Japan). The size of hematoma in ICH subjects was also measured by analyzing the image of computed tomography using the 3D software.

Clinical Evaluation

A complete medical history was obtained from each patient or a family member in cases where the patient was aphasic or unconscious. Physical examinations including heart rate, systolic blood pressure, and diastolic blood pressure were performed at admission. Risk factors were determined as follows: hypertension (treatment with antihypertensive medication or documented systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg before admission), diabetes mellitus (treatment with antidiabetic medication or diagnosis of diabetes during hospital stay), hyperlipidemia (treatment with lipid-lowering medication or diagnosis during hospital stay), and smoking at present or in the past. Neurological deficits were assessed using the National Institutes of Health Stroke Scale (NIHSS) (*17*) at admission.

Echocardiography

Standard M-mode, two-dimensional and color Doppler imaging were performed in the parasternal and apical views using an APLIO XV echocardiograph machine (Toshiba Medical

Table 1. Clinical Characteristics of the Subjects upon Admission

	LAA (n=27)	SAO (n=27)	ICH (n=25)	CT (n=26)	p value
Age (years)	74±8	70±8	68±13	67±12	0.10
Gender (female/male)	8/19	11/16	14/11	14/12	0.19
BMI (kg/m^2)	24.3±3.8	23.2±2.9	22.1±4.2	23.3±3.2	0.19
Systolic BP (mmHg)	160±20	155±22	165±26	150±26	0.08
Diastolic BP (mmHg)	88±15	88±15	94±14	86±13	0.26
Heart rate (beats/min)	74±13	70±14	75±13	74±12	0.41
Blood chemistry					
Sodium (mEq/L)	141±3	142±2	141±4	141±3	0.89
Creatinine (mg/dL)	0.70±0.17	0.66±0.15	0.61±0.17	0.65±0.20	0.25
Creatine kinase (IU/L)	170±137	123±109	149±92	104±47	0.08
Risk factors					
Hypertension (+/–)	19/8	18/9	18/7	16/10	0.86
Diabetes mellitus (+/–)	11/16	10/17	6/19	4/22	0.16
Hyperlipidemia (+/–)	10/17	10/17	5/20	5/21	0.27
Smoking (+/–)	11/16	7/20	8/17	9/17	0.71
Antihypertensive drugs (+/–)	10/17	11/16	8/17	13/13	0.60
Ca antagonist (n (%))	5 (19)	10 (37)	5 (20)	10 (38)	0.22
ACEI or ARB (n (%))	8 (30)	6 (22)	4 (16)	5 (19)	0.67
α-Blocker (n (%))	1 (4)	2 (7)	0 (0)	2 (8)	0.53
β-Blocker (n (%))	1 (4)	2 (7)	2 (8)	2 (8)	0.91
Diuretic (n (%))	3 (11)	1 (4)	0 (0)	1 (4)	0.29
NIHSS	7±6	3±2	14±10*		<0.0001

Values represent the means±SD. LAA, large-artery atherosclerosis; SAO, small-artery occlusion; ICH, intracerebral hemorrhage; CT, control; BMI, body mass index; BP, blood pressure; NIHSS, the National Institutes of Health Stroke Scale; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. *p<0.05 *vs*. LAA and SAO.

Table 2. Echocardiographic Parameters of the Subjects in This Study

	LAA	SAO	ICH	p value
LA dimension (mm)	35.7±4.9	34.7±5.5	31.8±6.3	0.10
Septal thickness (mm)	11.1±1.8	10.9±2.3	11.0±1.5	0.70
LVPW thickness (mm)	10.4±1.6	10.2±1.7	10.6±2.0	0.75
LVED diameter (mm)	45.7±5.6	46.0±5.5	42.9±4.9	0.12
LVES diameter (mm)	27.2±5.5	27.2±4.8	26.2±4.5	0.53
LV ejection fraction (%)	70.8±9.6	72.4±6.1	68.9±6.4	0.28
LV mass index (g/m^2)	126±26	130±33	126±31	0.89
E/*A*	0.68±0.17	0.70±0.20	0.65±0.12	0.76
Deceleration time (ms)	264±59	258±50	264±69	0.88

Values represent the means±SD. LAA, large-artery atherosclerosis; SAO, small-artery occlusion; ICH, intracerebral hemorrhage; LA, left atrium; LVPW, left ventricular posterior wall; LVED, left ventricular end-diastolic; LVES, left ventricular end-systolic; LV, left ventricular; *E*/*A*, ratio of peak early to peak atrial velocity.

Systems, Tochigi, Japan). Left atrial dimension, left ventricular septal and posterior wall thickness, and left ventricular chamber dimension were measured according to the guidelines of the American Society of Echocardiography (*18*). Left ventricular ejection fraction (LVEF) was calculated by the Teichholz's method (*19*). Left ventricular mass was calculated according to Devereux (*20*) and normalized for body surface area (left ventricular mass index). Peak early velocity (E velocity), peak atrial velocity (A velocity), peak early-to-peak atrial velocity (*E*/*A*) ratio, and deceleration time were measured from the transmitral Doppler flow. Echocardiographic findings were interpreted by a cardiologist who had no knowledge of the other data including the plasma BNP levels.

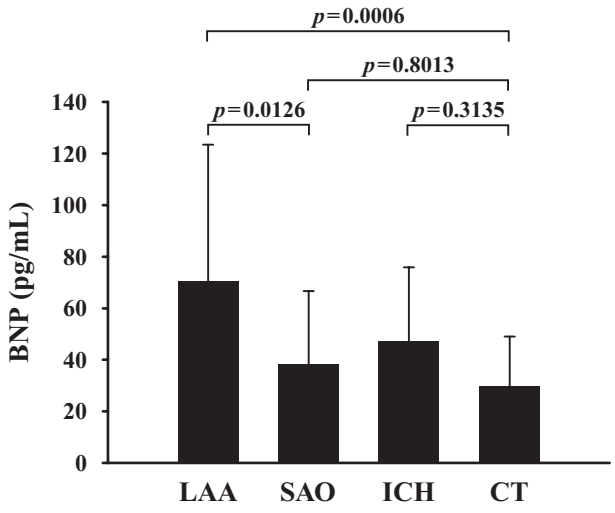

Fig. 1. *Comparison of plasma brain natriuretic peptide (BNP) levels among the patient groups upon admission. LAA indicates large-artery atherosclerosis; SAO, small-artery occlusion; ICH, intracerebral hemorrhage; CT, control. Values represent the means±SD.*

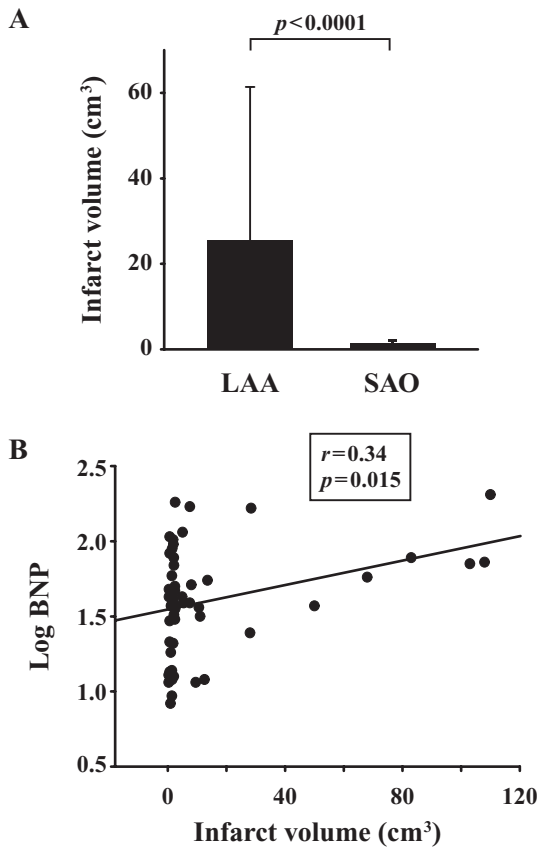

Fig. 2. *A: Comparison of brain infarct volume between the patients with large-artery atherosclerosis (LAA) and small-artery occlusion (SAO) upon admission. Values represent the means±SD. B: Relationship between plasma log brain natriuretic peptide (BNP) levels and brain infarct volume in acute ischemic stroke (LAA and SAO) at admission.*

Blood Sampling and BNP Measurement

Blood samples were taken from all subjects at admission in the emergency room before infusion therapy and 1 month later. The samples for BNP were obtained in chilled EDTA tubes and centrifuged at 4°C for 10 min. The plasma was then collected and stored at −70°C until assaying. BNP was assayed by Special Reference Laboratories, Inc. (Tokyo, Japan) using chemiluminescent enzyme immunoassays. Blood chemistry was analyzed in the hospital chemistry laboratory using standard techniques.

Statistical Analysis

All data are expressed as the means±SD. Differences between two groups were compared with the Mann-Whitney *U*-test. Differences among three or four groups were compared with the Kruskal-Wallis one-way analysis of variance followed by Scheffe's test for multiple comparisons. The χ^2 test was used for categorical variables. Because plasma BNP levels were not normally distributed, the value of BNP was logarithmically transformed for statistical analysis. A linear regression analysis was performed to examine the correlations between the plasma log BNP levels and infarct volume. The Spearman's rank correlation was used to determine the strength of association between the plasma log BNP levels and NIHSS. A multiple linear regression analysis was performed to determine the independence of association with other variables. Differences were considered significant when p values were <0.05.

Results

Profiles of the Study Patients

Table 1 shows clinical characteristics of the four groups on admission. Age, gender, body mass index, systolic and diastolic blood pressures, heart rate, serum sodium, creatinine, creatine kinase, and risk factors were not different among the four groups. In addition, there was no significant difference in the ratio of antihypertensive medications before admission among all groups, although half of all patients (55%) treated with antihypertensive drugs took two or more kinds of medication. NIHSS was significantly higher in the ICH group than in the LAA and SAO groups.

Echocardiographic Findings

Table 2 shows echocardiographic parameters of the patient

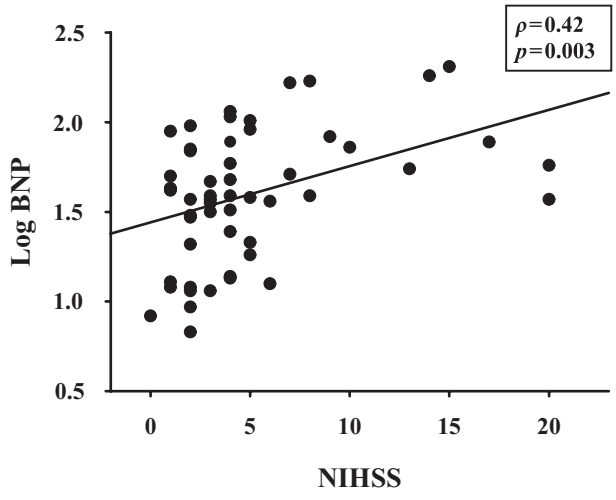

Fig. 3. *Relationship between the plasma log brain natriuretic peptide (BNP) levels and the National Institutes of Health Stroke Scale (NIHSS) in acute ischemic stroke (LAA and SAO) upon admission (Spearman test).*

groups. No significant differences in the parameters including left atrial dimension, LVEF, and left ventricular mass index were found among the LAA, SAO, and ICH groups.

Plasma BNP Levels

As shown in Fig. 1, the plasma BNP level at admission was significantly greater in LAA than in SAO and CT (70.6±53.9 *vs*. 38.2±28.4 and 28.5±19.9 pg/mL, respectively, both $p<0.05$). The BNP level in ICH (47.3±28.6 pg/mL) was not significantly different from that in CT. In the LAA group, there was no difference in the plasma BNP levels between supratentorial ($n=21$) and subtentorial ($n=6$) lesions (69.3±52.8 and 75.4±62.3 pg/mL, respectively). After 1 month, the plasma BNP level was significantly decreased in all groups, and was similar among LAA, SAO, and ICH (26.3±21.7, 21.0±14.4, and 21.6±13.5 pg/mL, respectively). In addition, the BNP level in the CT group on admission did not significantly differ from those in the LAA, SAO, and ICH groups after 1 month.

Brain Infarct Volume and Its Relationship with Plasma BNP Level in Acute Ischemic Stroke

As shown in Fig. 2A, brain infarct volume was significantly greater in LAA than in SAO (25.5±35.8 *vs*. 1.3±0.7 cm^3, $p<0.0001$). Moreover, as shown in Fig. 2B, the plasma BNP level at admission was positively correlated with brain infarct volume (mean 13.9±28.3 cm^3, $r=0.34$, $p=0.015$) in acute ischemic stroke (LAA and SAO).

Table 3. Multivariate Regression Analysis for Plasma Log BNP in Acute Ischemic Stroke (LAA and SAO) (Model 1)

	Coefficient (β)	SEM	p value
Age	0.202	0.006	0.15
Gender (male=1)	−0.195	0.130	0.29
BMI	−0.157	0.019	0.38
Systolic BP	0.269	0.003	0.10
Heart rate	−0.297	0.004	0.09
Serum creatinine	0.282	0.373	0.10
Serum creatine kinase	0.218	0.0004	0.12
Deceleration time	0.111	0.001	0.47
LV ejection fraction	−0.072	0.007	0.66
LV mass index	0.028	0.002	0.87
Infarct volume	0.433	0.002	0.03
NIHSS	0.140	0.018	0.53

Model 1 is shown, which includes both infarct volume and NIHSS. Abbreviations as in Tables 1 and 2. The value of BNP was logarithmically transformed.

Relationship between Plasma BNP Level and Stroke Severity

As shown in Fig. 3, the plasma BNP level in acute ischemic stroke (LAA and SAO) was positively correlated with the NIHSS (mean 5±4, $\rho=0.42$, $p=0.003$) at admission.

The size of hematoma in ICH subjects (25.2±30.8 cm^3) was not correlated with the plasma BNP level at admission ($p=0.20$). There was no relationship between the plasma BNP levels and the NIHSS ($p=0.95$) in the ICH group at admission.

Determinants of Plasma BNP Level in Acute Ischemic Stroke

A multiple linear regression analysis was performed to evaluate the independent determinants of the plasma BNP level in acute ischemic stroke (LAA and SAO). As shown in Table 3, brain infarct volume was an independent contributor to the plasma BNP level in acute ischemic stroke at admission (model 1). Since infarct volume correlated positively with NIHSS and it was necessary to avoid multicollinearity problems, we further analyzed these variables separately. When infarct volume or NIHSS was added separately (model 2 or 3) instead of together, infarct volume or NIHSS was an independent contributor to the plasma BNP level in acute ischemic stroke ($\beta=0.515$, SEM=0.002, $p=0.001$; and $\beta=0.464$, SEM=0.014, $p=0.007$, respectively). The other 10 variables were not independent factors in any of the three models. Each of the models, 1, 2, and 3, explained 48.9%, 48.3%, and 44.4% of the variability of log BNP, respectively.

Discussion

Elevated Plasma BNP Levels in LAA Independently of Heart Disease

Plasma BNP levels are elevated in patients with structural heart diseases or left ventricular dysfunction. Recent studies have shown that plasma BNP is also increased in acute ischemic stroke presumably due to myocardium damage or elevated blood pressure in the acute phase (*8*, *10*). The present study clearly showed that even after careful evaluation and exclusion of heart diseases, the plasma BNP level at admission was significantly higher in LAA than in SAO and CT, although no significant difference was found in the echocardiographic parameters and in blood pressure on admission among the groups. The facts that the plasma BNP levels in all CVD groups at 1 month after the onset were decreased and were similar to those in the CT group on admission seem to justify our evaluation and exclusion of structural or preexisting heart diseases in these subjects. Additionally, multivariate regression analysis for plasma BNP showed no relationship with echocardiographic parameters and blood pressure. Moreover, the plasma BNP level in the ICH group was not as high as that in the LAA group, despite the fact that systolic and diastolic blood pressures in the ICH group were rather higher than those in the LAA group. These findings suggest that the transient elevation of plasma BNP in patients with LAA is independent of heart diseases and blood pressure in the acute phase.

Brain Ischemia and Circulating BNP

Recent reports showed that hypoxia increases cardiac BNP gene expression in pigs and circulating BNP levels in humans, and occlusion of the middle cerebral artery stimulates BNP mRNA expression in rat brain tissues (*6*, *21*, *22*). Moreover, the human BNP gene promoter region contains a hypoxia-inducible factor (HIF)-1 binding site and BNP gene expression is activated by HIF-1 (*23*). In this context, considerable attention should be paid to the positive correlation between brain infarct volume and the plasma BNP level in acute ischemic stroke in this study. Furthermore, brain infarct volume was an independent predictor of the circulating BNP level in acute ischemic stroke by multivariate regression analysis (models 1 and 2). The mechanism by which the plasma levels of BNP are increased in patients with acute ischemic stroke independently of heart diseases is less obvious and cannot be fully elucidated from the present reports. However, our results raise the possibility that the infarct or ischemic area in the brain could be a potential source of circulating BNP. Iltumur *et al*. showed that plasma NT-proBNP levels in patients with acute ischemic stroke correlated negatively with LVEF (*10*). Importantly, some patients had elevated NT-proBNP levels even if their LVEF was preserved normally. In addition, recent studies have shown that elevated plasma NT-proBNP levels are involved in the pathogenesis of brain edema in ischemic and hemorrhagic strokes (*24*, *25*). These findings suggest that the ischemic brain itself may also release NT-proBNP into the circulation. It has been reported that S-100β protein, a calcium-binding protein abundant in glial and Schwann cells, is increased in blood and cerebrospinal fluid (CSF) after ischemic stroke and its plasma concentration correlates positively with the size of infarct volume in humans (*26*, *27*). Thus, it may be important to investigate whether the concentration of BNP in CSF would be increased after brain infarction or ischemia and BNP released from the ischemic brain tissues would exert a neuroprotective effect around the ischemic area.

Clinical Significance of Plasma BNP Level in Acute Ischemic Stroke

The prognostic value of BNP has been demonstrated in patients with CHF and acute myocardial infarction (*28*, *29*). More recent studies have shown that the plasma levels of BNP or NT-proBNP in the acute phase of ischemic stroke predict post-stroke mortality (*7*, *9*). In this study, significant correlations were found between the plasma BNP level and the NIHSS in acute ischemic stroke at admission. In addition, the NIHSS is an independent determinant of the plasma BNP level in acute ischemic stroke by multivariate regression analysis (model 3). Since higher plasma BNP levels reflect a greater infarct area, this correlation is compatible with the clinical manifestations. Thus, the plasma BNP level can be a clinically useful marker indicative of the severity of acute ischemic stroke. Further long-term observations will clarify the prognostic value of BNP in ischemic stroke patients independently of heart diseases.

Our data show that the plasma BNP level in the ICH group at admission was not different from that in the CT group, although NIHSS was significantly higher in the ICH group than in the LAA and SAO groups. In addition, no relationships between the plasma BNP level and hemorrhage size or NIHSS were found in the ICH group. Together, these data suggest that BNP seems to be inappropriate for use as a marker of the severity in ICH subjects, although it is not excluded that hematoma might cause infarction in the area adjacent to hemorrhagic lesion.

Study Limitations

There are some limitations in this study. First, the small sample size obliges us to be cautious in the generalization of our results. Second, our findings can be applied to only limited numbers of CVD patients who have no obvious heart diseases and exhibit normal renal function, although minor cardiac abnormalities may not have been detected in some patients in the study. Furthermore, CE infarction should be excluded. Third, we cannot exclude the possibility that there are other

important explanatory variables which may contribute to the plasma BNP level, since our three multivariate regression models explained only around 49% of the total variance. Finally, we cannot completely exclude acute myocardial damage due to increased sympathetic activity and catecholamines in the acute phase of ischemic stroke leading to elevation of the plasma BNP level (*10*, *30*), because we measured only creatine kinase and not catecholamines, creatine kinase-MB isoenzyme, or more specific biochemical markers of myocardial injury, cardiac troponin T or I. However, it is reported that these markers are elevated in only a small group if any of the acute ischemic stroke patients (*7*, *31*). More research with larger populations and additional data on cardiac markers are needed to confirm our initial findings.

In conclusion, the present study provides the first evidence that the plasma BNP level transiently increases in patients with LAA independently of heart diseases, and can be a useful biomedical marker reflecting the infarct volume and the severity of acute ischemic stroke. More basic and clinical studies will be required to clarify the possible mechanism underlying the transient increase in BNP and its potential roles in acute ischemic stroke.

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