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Brain Natriuretic Peptide is a Predictor of Cardiac Thrombus in Critically Ill Acute Ischemic Stroke Patients

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Abstract

CONTEXT: Plasma brain natriuretic peptide (BNP) levels are elevated in patients with acute ischemic stroke, particularly when accompanied by atrial fibrillation (AF). Plasma BNP might be a useful marker of vulnerability to thromboembolism in non-valvular AF patients.

AIM: The aim of the present study was to assess whether the BNP level can serve as a biomarker of the left atrial (LA) thrombus in AF patients with acute ischemic stroke.

SETTINGS AND DESIGN: This was a multicenter prospective cohort study.

PATIENTS AND METHODS: Thirty AF patients with acute ischemic stroke were included in the study. Their transesophageal echocardiography (TEE) and BNP were assessed.

RESULTS: There was a positive significant relation between serum BNP levels and LA thrombus detection by TEE. BNP with a cutoff value >498 pg/l can be used as a diagnostic biomarker for the presence of the LA thrombus. A significant positive correlation existed between serum BNP and LA diameter. Furthermore, a statistically significant positive correlation between serum BNP and AF rate and duration was found in all patients. In addition, a statistically significant inverse correlation was detected between serum BNP and direct bilirubin, international normalized ratio, and albumin. A statistically significant positive correlation existed between serum BNP and prothrombin concentration.

CONCLUSION: BNP can be a good diagnostic biomarker for the detection of the LA thrombus in chronic AF patients with acute ischemic stroke.

Introduction

Atrial fibrillation (AF) patients with ischemic stroke or transient ischemic attacks (TIAs) are at high risk for recurrent stroke. Patients with the left atrial (LA) thrombus are at particularly high risk for thromboembolic events, the incidence of which can be reduced by anticoagulant agents.

Therefore, early identification of the LA thrombus in acute ischemic stroke is important to prevent further brain ischemia [1].

Although transesophageal echocardiography (TEE) is a useful clinical tool for identifying actual thrombi and visualizing spontaneous echo contrast in AF patients, its semi-invasive nature precludes its application for patients with acute stroke [2].

Brain natriuretic peptide (BNP) is 32 amino acids polypeptide with a 17 amino acid ring structure that was named after isolation from the porcine brain in 1988. It is a diuretic and vasodilatory factor that is released mainly from the ventricular myocardium. BNP was shown to be a sensitive marker of congestive heart failure. Plasma BNP levels are elevated in patients with acute ischemic stroke, particularly when accompanied by AF. Plasma BNP might be a useful marker of vulnerability to thromboembolism in non-valvular AF patients [3].

Aim of the work

The aim of the present study was to assess whether BNP levels can serve as a diagnostic biological marker of thrombus in AF patients with acute ischemic stroke. Study group – it consisted of 30 chronic AF patients who had acute ischemic stroke.

The study group was further divided into subgroups according to the results of TEE into either TEE positive or TEE negative. All participants were subjected to a full and careful history taking and clinical examination and echocardiography. Echocardiography was carried out using transthoracic echocardiography with M mode, two D mode, and Doppler study. In TEE, the key view is the two-chamber view to see the LA appendage (LAA), and it can be useful to study the appendage at ~90° to this view to see the pectinate muscles in more details. The scan plane can be rotated

to ~140° while maintaining the appendage in the center of the image [4].

Laboratory tests

Samples of BNP were withdrawn on the same day of doing TEE and were measured using the fluorescent immune-sorbent assay. The test principle is as follows:-

The microtiter plate provided in the kit comes pre-coated with an antibody specific to BNP. Samples are then added to the appropriate microtiter plate wells with a biotin-conjugated antibody specific to BNP. Next, avidin conjugated to horseradish peroxidase is added to each microplate well and incubated. After 3,3′,5,5′-tetramethylbenzidine substrate solution is added, only those wells that contain BNP, biotin-conjugated antibody, and enzyme-conjugated avidin exhibit a change in color. The enzyme-substrate reaction is terminated by the addition of a sulfuric acid solution and the color change is measured spectrophotometrically at a wavelength of 450 ± 10 nm. BNP concentration in the samples is then determined by comparing the optical density of the color of the samples to the standard curve [5].

Statistical data

Data were analyzed on an IBM computer using Statistical Package for the Social Sciences, version 12 as follows:

(1) Quantitative variables were described as mean, standard deviation (SD), and range.
(2) Qualitative variables were described as number and percentage.
(3) The Chi-square-test was used to compare qualitative variables between groups.
(4) The unpaired t-test was used to compare quantitative variables, in parametric data (SD <50% mean).
(5) The one-way analysis of variance test was used to compare more than two groups as regard quantitative variables.
(6) Spearman's correlation coefficient test was used to rank variables versus each other positively or inversely.
(7) Receiver operator characteristic curve was used to find out the best cutoff value and validity of a certain variable [6].

Results

There was a positive significant relation between serum BNP levels and presence of the LA thrombus, as documented by TEE. BNP with a cutoff value >498 pg/l can be used as a diagnostic biomarker for the presence of the LA thrombus.

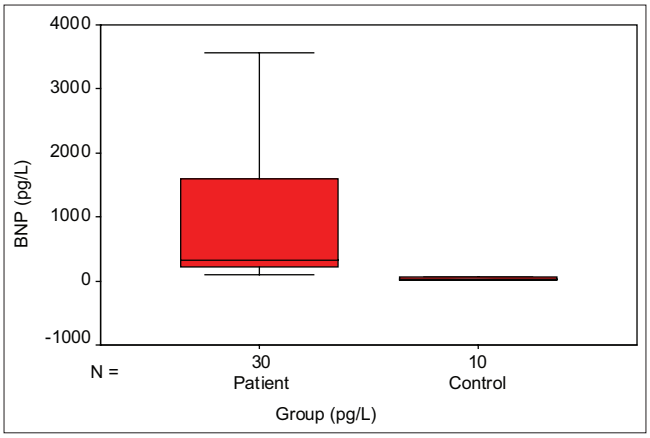

Figure 1: Patients with transesophageal echocardiography (TEE)-positive group having statistically significantly higher level of serum brain natriuretic peptide compared with the TEE-negative group (p < 0.001)

A significant positive correlation existed between serum BNP and LA diameter. In addition, a statistically significant positive correlation between serum BNP and AF rate and duration was found in all patients.

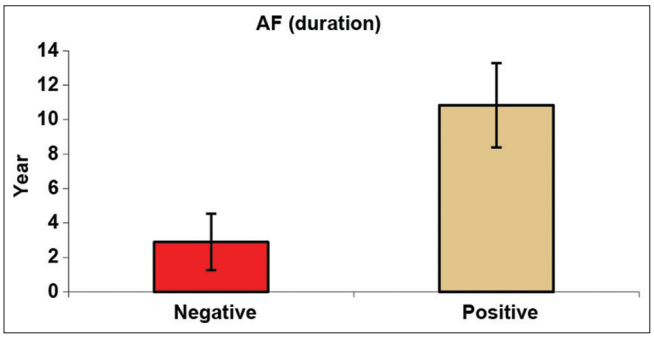

Figure2: Correlation between serum brain natriuretic peptide levels and atrial fibrillation duration

A statistically significant inverse correlation was detected between serum BNP and direct bilirubin, international normalized ratio, and albumin. A statistically significant positive correlation existed between serum BNP and prothrombin concentration (Figures 1-4 and Tables 1-11).

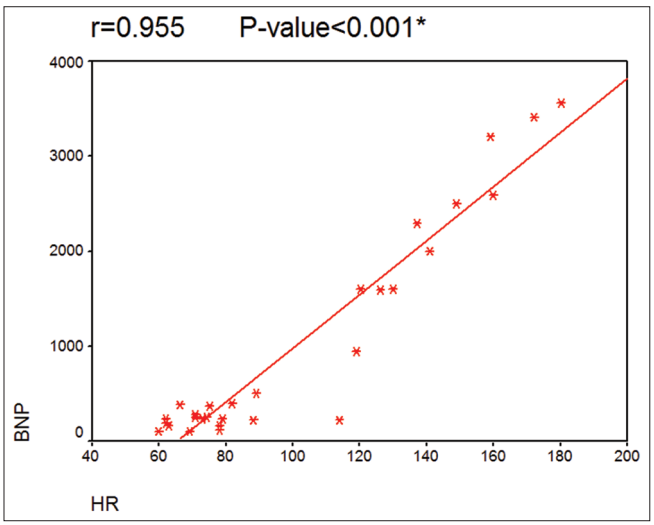

Figure 3: Validity of serum brain natriuretic peptide in the prediction of transesophageal echocardiography result

Discussion

The current study agrees with Okada *et al.* who were trying to find a relation between serum BNP levels and LA thrombus in chronic AF patients admitted with acute ischemic stroke (within 7 days) of an ischemic stroke or TIA, serum BNP was withdrawn at the day of TEE; the results were as follows:

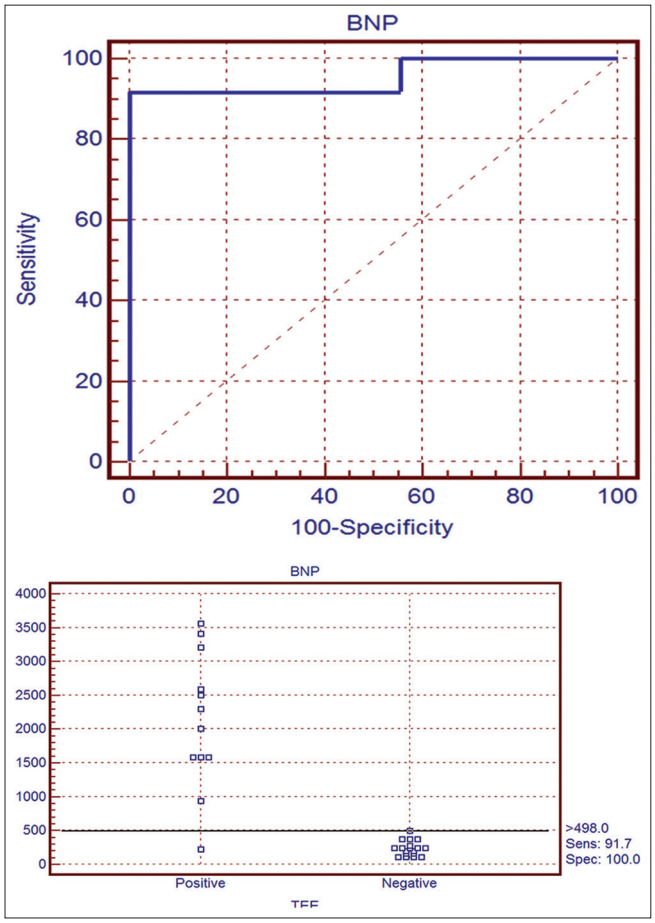

Figure 4: Validity of serum brain natriuretic peptide in the prediction of transesophageal echocardiography result

Table 1: Demographic data of patients

Variables	Patient (%)	Control (%)	p-value
Gender			
Female	16 (53.33)	3 (30)	0.195
Male	14 (46.67)	7 (70)	
Age (Mean±SD)	58.7±10.462	28.7±5.774	<0.001*

SD: Standard deviation.

TEE-positive group (n = 17), serum BNP was higher compared with the TEE-negative group (n = 50) (307.3 ± 270.6 vs. 146.5 ± 119.5 pg/l, respectively) (p = 0.012).

Table 2: Distribution of the studied cases as regard clinical data

Clinical data	n (%)
Smoking	14 (46.67)
IHD	8 (26.67)
HTN	14 (46.67)
DM	21 (70)
Dyslipidemia	21 (70)

DM: Diabetes mellitus, HTN: Hypertension, IHD: Ischemic heart disease.

Furthermore, they found that TEE-positive patients had statistically significant higher age than those of TEE-negative patients (76.5 ± 9.5 vs. 55.4 ± 11.7 years, respectively) (p ≤ 0.001).

Table 3: Distribution of the studied patients as regard transesophageal echocardiography results (left atrial thrombus)

TEE	n (%)
Negative	18 (60)
Positive	12 (40)
Total	30 (100)

TEE: Transesophageal echocardiography.

This comes in agreement with the findings of our study: The mean age in the TEE-positive group was 68.167 ± 9.20 years compared with 52.389 ± 5.14 in the TEE-negative group (p < 0.001). A positive correlation existed between serum BNP and age (r = 0.562 and p < 0.001) [7].

Table 4: Serum brain natriuretic peptide in patients with acute ischemic stroke

Group	BNP (pg/L)				
	Range	Median	Interquartile range	Mean rank	p-value
Patient	103.000–3557.000	322.500	1491.500	25.500	<0.001*
Control	8.00–63.000	27.000	45.500	5.500	

BNP: Brain natriuretic peptide.

Doukky *et al.* conducted a retrograde cohort study of 297 consecutive cases with non-valvular AF who underwent a clinically indicated TEE for the LA thrombus detection. They aimed to investigate whether the plasma BNP is predictive of the LAA thrombus and stroke or not. Nineteen (6.4%) patients were found to have LA thrombus by TEE and the remaining 278 (93.6%) were free of LA thrombus.

Table 5: Comparison between transesophageal echocardiography positive and negative groups as regard serum brain natriuretic peptide

Group	BNP (pg/L)		p-value
	Range	Mean±SD	
Negative	103.000–489.000	237.611±112.014	<0.001*
Positive	825.000–43757	2125.333±1005.918	

BNP: Brain natriuretic peptide.

There was a stepwise increase in the prevalence of the LA thrombus with an increasing BNP level. All patients with positive TEE had serum BNP of at least 500 pg/l and a decreased heart rate. However, in their study, there was no statistically significant difference as regard mean age in the TEE-positive group (n = 19) and the TEE-negative group (n = 278) (66 ± 13 vs. 62 ± 14 years, respectively) (p = 0.37) [8].

Table 6: Comparison between normal and abnormal left atrial diameter and serum brain natriuretic peptide

LA echo	BNP (pg/L)				p-value
	Range	Median	Interquartile range	Mean rank	
Normal	103.000–195.000	118.000	56.000	4.000	<0.001*
Abnormal	218.000–3557.000	498.000	2050.000	19.000	

BNP: Brain natriuretic peptide, LA: Left atrial.

Sakai *et al.* studied 221 patients (141 men; mean age: 72.9 years) to evaluate the role of BNP in distinguishing cardioembolic (CE) stroke from non-CE stroke. The median of the NIHSS score on admission was 6 (2–15.75). The mean ± SD time interval from stroke onset to blood sample collection was 8.2 ± 7.4 h, and the mean ± SD BNP level was 214.5 ± 358.3 pg/ml.

Table 7: Correlation between serum brain natriuretic peptide and age, left atrial diameter, atrial fibrillation duration, and atrial fibrillation rate

Correlations	BNP (pg/L)	
	R	p-value
Age (years)	0.562	0.001*
LA echo	0.872	<0.001*
AF (duration)	0.902	<0.001*
HR (beat/min)	0.955	<0.001*

HR: Heart rate, AF: Atrial fibrillation, LA: Left atrial.

According to the results of BNP, they divided the patients into two groups: The high BNP level group, which included 81 (36.7%) patients and the low BNP level group, which included 140 (63.3%) patients. They found that the patients of the high BNP level group were of CE origin, mostly AF with variable types. They also found that there was a statistically significant difference between the high BNP level (CE positive) group and the low BNP level (CE negative) group as regard age (77.7 ± 12.0 vs. 70.1 ± 12.0, respectively) ($p < 0.001$) [9].

Table 8: Correlation between serum brain natriuretic peptide and laboratory data

Correlations	BNP (pg/L)	
	R	p-value
Bil T (mg/dL)	−0.350	0.058*
Bil D (mg/dL)	−0.392	0.032*
PT (s)	−0.348	0.059*
INR	−0.373	0.042*
PC (%)	0.442	0.014*
Uric acid (mg/dL)	0.350	0.058*
Albumin (g/dL)	−0.760	<0.001*

BNP: Brain natriuretic peptide.

Okada *et al*. [6] found no effect of sex on the stroke or thrombus formation or the serum BNP level.

Table 9: Validity of serum brain natriuretic peptide in the prediction of transesophageal echocardiography result

ROC curve					
Cutoff	Sens.	Spec.	PPN	NPV	Accuracy
>498*	91.7	100.0	100.0	94.7	0.954

That BNP is considered highly valid in prediction with the left atrial thrombus, with sensitivity of 91% at cutoff value 498 pg. NPV: Negative predictive value, PPV: Positive predictive value, ROC: Receiver operating characteristic.

However, Sakai *et al.* found a significant difference as regard sex between the high and low BNP level groups. The frequency of the female sex in the high BNP group was 44.4% compared with 31.4% for the low BNP group ($p < 0.001$) [9].

Table 10: Effect of atrial fibrillation duration on the serum level of brain natriuretic peptide according to the equation BNP=−406.764+230.681 AF duration, with the R square of 81%

Model	Unstandardized coefficients	Standardized coefficients		p-value	R-square
	B	Std. error	Beta		
Constant	−406.764	155.577		0.014*	81.4%
AF (duration)	230.681	20.852	0.902	<0.001*	

BNP: Brain natriuretic peptide, AF: Atrial fibrillation.

In their study, Okada included 17 TIA patients, with a mean age of 76.5 + 11.1 years. There was a positive correlation ($r = 0.872$) between LA diameter and serum BNP levels with $p < 0.001$. This means that serum BNP is elevated with the LA dilatation, which increased the risk for LA thrombus [7].

Table 11: Effect of LA diameter on the serum brain natriuretic peptide level according to the equation BNP=−6130.826+1476.889 LA diameter, with R square of 76%

Model	Unstandardized coefficients	Standardized coefficients		p-value	R-square
	B	Std. error	Beta		
Constant	−6130.826	763.304		<0.001*	76%
LA echo	1476.889	156.810	0.872	<0.001*	

BNP: Brain natriuretic peptide, LA: Left atrial.

In agreement with the results of the present study, Doukky *et al*. [8] also showed that the BNP level had highly statistically significant positive correlation with LA size (coefficient $r = 0.33$ and $p = 0.002$). Moreover, Obel *et al.* showed that an increasing ventricular rate was associated with significantly lower peak inflow, peak outflow, mean inflow, and mean outflow velocities as well as with a lower time velocity interval of the LAA filling and emptying velocities. This effect was noted at rates of 60 beats/min compared with both 120 and 150 beats/min [10], [11].

The findings of the present study were in agreement with those of Shimizu *et al.*; they assessed a possible relationship between LAA function and plasma BNP levels in non-valvular AF. The study consisted of 34 patients with chronic non-valvular AF (age: 69 ± 9 years) who underwent a TEE study and plasma BNP measurement. The patients were divided into two groups: Patients with and patients without a history of CE events (stroke) or echocardiographic evidence of thrombus into the embolic positive (E positive) group and the embolic negative (E negative) group, respectively. The patients of the E-positive group demonstrated greater impairment of the LAA velocity and higher plasma BNP levels than did those of the E-negative group. There was a statistically significant difference as regard LAA velocity (LAA velocity of 12 ± 6 in the positive group vs. 31 ± 17 cm/s in the negative group, $p < 0.05$) [8], [12].

The findings of the current study were in agreement with those of Okada *et al.* who reported that the TEE-positive group had statistically significant higher serum BNP levels compared with the TEE-negative group (307.3 ± 270.6 vs. 146.5 ± 119.5 pg/l, respectively; $p = 0.012$). This was in agreement with our results where a statistically significant difference was found between serum BNP in TEE-positive and TEE-negative groups (2125.333 ± 1005.918 vs. 237.611 ± 112.046 pg/l, respectively; $p < 0.001$) [7].

In addition, the findings of the present study were in agreement with those of Doukky *et al.* who found that serum BNP was highly elevated in patients with LA thrombus TEE positive (n = 19) compared with patients with LA thrombus TEE negative (n = 278), with a statistically significant difference (1949 ± 1787 vs. 819 ± 1067 pg/l, respectively; $p = 0.001$). They concluded that the serum BNP level is predictive of LA thrombus in patients with non-valvular AF and may have a better discriminatory capacity than that of the CHADS2 and CHADS2-VASc [8].

Sakai *et al.* found that the patients in the high BNP group were of CE in origin, mostly AF with variable types. CE occurred in 59 (72.8%) patients in the high BNP group (n = 81) and in 17 (12.1%) patients in the low BNP group (n = 140), with p < 0.001 [8].

Of the 21 patients without CE who had high BNP levels, seven had chronic renal failure, five had old myocardial infarction, and two were cardiomyopathic (22 patients of high BNP group were of non-CE stroke and 123 patients of the low BNP group were of non-CE stroke). A BNP level of 142.5 pg/ml was identified as the optimal cutoff value with a sensitivity of 77.6% and specificity of 84.8%. This is in agreement with the findings of the present study; however, a higher cutoff level of more than 498 pg/ml increased sensitivity to 91.7% and specificity to 100% [9].

Shimizu *et al.* reported that the atrium is the main source of BNP in AF patients without overt heart failure. Thirteen chronic non-valvular AF patients with a history of CE events (stroke) or echocardiographic evidence of thrombus (E-positive group) were compared with 21 AF patients without complications (neither echocardiographic evidence of the LA thrombus nor any CE events) (E-negative group). The result of their study showed that the patients of the E-positive group demonstrated greater impairment of the LAA velocity and higher plasma BNP levels than did those of the E-negative group. Their study showed a statistically significant difference as regard serum BNP between the two groups (126 ± 53 vs. 86 ± 45 ng/l; p < 0.05). They concluded that BNP was a significant predictor of thromboembolism. This is in agreement with our results; a statistically significant difference was detected in our study between serum BNP in TEE-positive and TEE-negative groups (2125.333 ± 1005.918 vs. 237.611 ± 112.046 pg/l, respectively; p < 0.001). Moreover, our results were in agreement with those of Maruyama *et al.* who studied 231 patients with acute ischemic stroke. The highest serum BNP level was found in patients with CE stroke due to AF. The BNP levels positively correlated with CHADS2 scores in AF patients (202 [120–385 pg/l]) with p < 0.001 [12], [13].

The results of the current study were in agreement with those of Zhixin *et al.* who studied 142 acute ischemic stroke patients and made their discharge diagnosis and stroke etiologic subtypes according to TOAST criteria: LAA, CE, small artery occlusion, stroke of other determined etiology, and stroke of other undetermined etiology. Of the 142 patients, 35.92% were diagnosed with LAA at discharge, 25.35% with CE, 27.46% with small artery occlusion, and 11.27% with stroke of other determined etiology or stroke of other undetermined etiology. Age, previous cardiac disease, AF, length of the stay, NIHSS on admission, and modified Rankin score on discharge were all significantly higher in the CE patients compared with those of other subtypes (p < 0.01). Moreover, the mean BNP concentration was significantly higher in the CE group than those of other subtypes (p < 0.001). The optimal cutoff value, sensitivity, and specificity of the plasma BNP concentration suitable to distinguish CE from non-CE were 66.5 pg/l, 75.0%, and 88.7%, respectively [14]. This study showed a good positive correlation among the study groups between serum BNP and AF duration with p < 0.001 and r = 0.902. A possible explanation could be that with increased AF duration, the LA becomes more and more dilated because of remodeling. The LA is the main source of BNP in chronic AF, and thus, its level increases with time.

Conclusion

BNP can be used as a good diagnostic biomarker for the presence of the LA thrombus in chronic non-valvular AF intensive care unit patients admitted with acute ischemic stroke.

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