

High serum levels of pro-brain natriuretic peptide (pro BNP) identify cardioembolic origin in undetermined stroke

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Abstract. *Background:* Stroke subtype diagnosis leads to specific therapies to reduce recurrences. Because nearly one third of patients remain with unknown etiology after a complete screening workup, we aim to investigate whether molecular markers of myocardial damage were associated with cardioembolic stroke and if they were useful to reclassify strokes of undetermined etiology.

Methods: We included 262 patients with first ischemic stroke within the first 12 hours. Stroke subtype was evaluated by TOAST criteria. Stroke of undetermined origin were reclassified into likely atherothrombotic or likely cardioembolic according to a predefined non-validated algorithm. Blood samples were obtained on admission to determine serum levels of molecular markers (pro-BNP, pro-ANP and CK-MB) of myocardial damage.

Results: Patients with cardioembolic infarct showed higher levels of pro-BNP, pro-ANP and CK-MB. Pro-BNP > 360 pg/mL was independently associated with cardioembolic stroke (OR: 28.51, CI95%: 5.90–136.75, $p < 0.0001$). Stroke etiology was undetermined in 82 patients (31%); 34 were reclassified as likely cardioembolic, 22 as likely atherothrombotic, and 26 remained as undetermined. Pro-BNP > 360 pg/mL was the only factor independently associated with likely cardioembolic stroke.

Conclusions: Pro-BNP levels higher than 360 pg/mL are associated with cardioembolic stroke and may be useful to reclassify undetermined strokes as of cardioembolic origin.

Keywords: Brain natriuretic peptide, cardioembolic stroke, ischemic stroke, ischemic stroke classification

1. Introduction

Stroke subtype diagnosis leads to specific therapeutic actions to reduce recurrences. TOAST criteria [1] are the most used criteria for stroke subtype classification, however, after a complete screening tool, nearly one third of patients remain without a specific etiology.

Several molecular markers, such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and cre-

atin kinase-MB (CK-MB), are increased in heart damage diseases, and are related with prognosis. Transient increased of CK-MB plasma levels are found in acute myocardial infarction [23], and high plasma levels of ANP and BNP have been associated with ventricular dysfunction and poor outcome in patients with acute myocardial infarction and congestive heart failure [19, 33].

These molecular markers have been also investigated in stroke patients. Some studies found that CK-MB levels increase after brain damage in absence of coronary heart disease, such as ischemic stroke, subarachnoid hemorrhage or cranial trauma [7,10,13,21]. High ANP levels have been found in stroke patients with

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atrial fibrillation compared to those with small vessel disease [25], and high BNP levels were found in stroke patients compared to healthy controls with similar risk factors, regardless infarct volume, stroke location and severity [9]. Recent studies found higher levels of BNP in patients with cardioembolic stroke [16,20], however, none have studied if these markers are useful to identify patients with possible cardioembolic stroke in undetermined etiology.

The objective of this study was to determine whether molecular markers of myocardial damage were associated with cardioembolic stroke and if they were useful to reclassify strokes of undetermined etiology.

2. Patients and methods

From January to June 2006, 372 consecutive patients with a first episode of ischemic stroke were prospectively evaluated within the first 12 hours from stroke onset. Patients in coma or with severe stroke (NIHSS > 20) ($n = 30$), previous disability (defined as mRS ≥ 2) ($n = 12$), severe systemic diseases (chronic inflammatory, infectious, or hematologic diseases, cancer and renal or liver failure) ($n = 26$), dementia or psychiatric diseases ($n = 8$), unstable cardiovascular disease ($n = 28$) including acute myocardial infarct, determined by clinical, electrocardiographic and biological changes (increased levels of troponin, mioglobin and CK-MB), or life expectancy of less than 3 months ($n = 6$) were excluded. A total of 262 patients were finally included in the study. The protocol was approved by local ethics committee and informed consent was given by patients or their relatives.

Demographic data (age, sex), previous history of high blood pressure, diabetes and heart disease, alcohol consumption and smoking habit were recorded. Stroke severity on admission was evaluated by the National Institute of Health Stroke Scale (NIHSS) score. Body temperature, blood pressure, serum glucose and fibrinogen levels, chest radiography and electrocardiogram were obtained on admission. Infarct volume in diffusion-weighted magnetic resonance imaging (DWI-MRI) was obtained using a manual tracing method within the first 12 hours from stroke onset. Blood samples for further determination of molecular markers (pro-ANP, pro-BNP and CK-MB) were drawn within 24 hours after hospitalization.

History of arterial hypertension (defined as evidence of at least two blood pressure measurements > 140/90 mmHg recorded on different days before

stroke onset, a physician's diagnosis or use of anti-hypertensive treatment), diabetes (fasting serum glucose levels ≥ 7.0 mmol/L, a physician diagnosis or use of diabetic medication), hyperlipidemia (serum cholesterol concentration > 12.2 mmol/L or use of medication), current smoking status and alcohol overuse (> 60 g/day) was determined at admission.

Stroke subtype was classified in atherothrombotic, cardioembolic, lacunar and undetermined according to TOAST criteria [1], once carotid and transcranial ultrasound study and echocardiogram were performed. Trained cardiologist blinded to clinical and biological data made echocardiography in patients in which no cardioembolic source was detected in electrocardiogram at admission ($n = 132$). For a secondary analysis, infarcts of undetermined etiology (both because no etiology was found after complete study or 2 causes were present) were reclassified according to the atherothrombotic and cardioembolic risk. We considered that the atherothrombotic risk was low when the patient was female, supraaortic arteries stenosis $\leq 50\%$, and no vascular risk factors were present; medium atherothrombotic risk in patients with ≤ 2 vascular risk factors and supraaortic arteries stenosis $\leq 50\%$; and high atherothrombotic risk when supraaortic arteries stenosis > 50%, subocclusive stenosis or intracranial stenosis and > 2 vascular risk factors. Cardioembolic risk was evaluated using CHADS₂ criteria [8], in which heart failure, high blood pressure, age ≥ 75 years and diabetes score 1 point, and previous stroke or TIA scores 2 point. Patients with score 0 were classified as low cardioembolic risk, score 1–2 as medium risk and score 3–6 as high risk. Patients with high atherothrombotic and low cardioembolic risk were reclassified as likely atherothrombotic, and patients with high cardioembolic and low atherothrombotic risk as likely cardioembolic. Patients with medium atherothrombotic and/or cardioembolic, high cardioembolic and atherothrombotic or low cardioembolic and atherothrombotic risk remain as undetermined.

2.1. Laboratory tests

Blood samples on admission were collected in glass chemistry test tubes, centrifuged at 3000 g for 10 minutes, and immediately frozen and stored at -80°C . Serum pro-BNP and CK-MB levels were measured by electrochemiluminescence immunoassay "ECLIA", ELECSYS 2010 System, Roche Diagnostics GmbH, Mannheim, Germany. Finally, serum levels of pro-ANP were measured with a commercially avail-

Table 1
Basal characteristics of patients according to stroke subtype, univariate analysis

	Atherothrombotic <i>n</i> = 44	Cardioembolic <i>n</i> = 100	Lacunar <i>n</i> = 36	Undetermined <i>n</i> = 82	<i>p</i>
Age, years	67.8 ± 9.5	72.3 ± 11.1	65.1 ± 12.6	68.1 ± 11.7	0.015
Female, %	31.8	50.0	38.9	36.6	0.133
History of hypertension, %	63.6	62.0	44.0	51.2	0.158
History of diabetes, %	36.4	14.0	22.2	17.1	0.017
Hypercholesterolemia, %	36.4	18.0	11.1	26.8	0.024
Smoker, %	31.8	18.0	22.0	19.5	0.294
Alcohol consumption > 40 g/day, %	9.1	2.0	0	7.3	0.004
Coronary heart disease, %	9.1	22.0	5.6	2.4	< 0.0001
Atrial fibrillation, %	0	50.0	11.1	4.9	< 0.0001
SBP, mm Hg	144.4 ± 26.1	151.2 ± 22.6	157.1 ± 24.3	150.9 ± 20.0	0.705
DBP, mm Hg	78.6 ± 11.7	79.9 ± 11.5	85.1 ± 16.4	80.1 ± 16.6	0.705
Body temperature, °C	36.2 ± 0.5	36.4 ± 0.3	36.3 ± 0.3	36.3 ± 0.3	0.120
Glucose, mg/dL	118.2 ± 32.5	126.1 ± 28.7	115.4 ± 23.9	131.3 ± 49.8	0.499
Fibrinogen, mg/dL	419.7 ± 142.3	443.9 ± 145.4	335.6 ± 62.9	371.2 ± 95.2	0.001
Basal NIHSS	12 [7, 17]	12 [8, 17]	6 [3, 8]	10 [6, 16]	< 0.0001
DWI volume at admission, cc	19.2 [5.0, 54.0]	25.4 [15.0, 48.0]	1 [0, 1.0]	24.5 [6.0, 68.0]	< 0.0001
Carotid stenosis >50%, %	77.3	0	5.6	4.9	< 0.0001
Carotid stenosis ≤50%, %	22.7	15.0	11.1	22.0	0.346
Intracranial stenosis, %	20.5	4.0	5.6	9.8	0.012
Pro-BNP levels (pg/mL)	64.4 [15.6, 250.7]	1131.5 [483.9, 1959.0]	151.7 [78.4, 355.8]	225.7 [110.5, 863.7]	< 0.0001
Pro-ANP levels (fmol/mL)	1020.2 [604.2, 2609.6]	3359.4 [1950.5, 7250.6]	1223.3 [451.0, 3058.1]	1377.8 [599.7, 4868.1]	< 0.0001
CK-MB levels (ng/mL)	1.90 [1.27, 2.46]	3.02 [2.23, 4.08]	2.23 [1.99, 2.74]	2.65 [2.03, 4.86]	< 0.0001

SBP: systolic blood pressure, DBP: diastolic blood pressure, DWI: diffusion-weighted image.

able quantitative enzyme-linked immunosorbent assay (ELISA) kits obtained from Biomedica GmbH, Vienna, Austria. Determinations were performed in an independent laboratory blinded to clinical and neuroimaging data. The intra-assay and interassay coefficients of variation were < 5% for NT-proBNP, pro-ANP and CK-MB determinations.

2.2. Statistical analyses

Results are expressed as percentages for categorical variables and compared using the chi-square test, and as mean (standard deviation), or median [quartiles] for the continuous variables. Comparison of baseline characteristics of the different groups was calculated by ANOVA. ROC curves were configured to establish cut-off points of molecular marker levels that optimally predicted the cardioembolic origin of stroke. Odds ratios were adjusted by significant variables in the bivariate analysis.

Values of *p* below 0.05 were considered to be statistically significant in all tests. The statistical analysis was conducted using SPSS 16.0 for Windows XP.

3. Results

We included 262 patients (69.8 ± 11.8 years, 58.7% male). Stroke subtype was classified as atherothrom-

botic in 44 patients (16.8%), cardioembolic in 100 (38.2%), lacunar in 36 (13.7%), and undetermined in 82 (31.3%).

Basal characteristics of patients are shown in Table 1. No differences in infarct volume were found between atherothrombotic and cardioembolic infarcts. Higher levels of pro-BNP, pro-ANP and CK-MB were found in patients with cardioembolic infarcts (Fig. 1).

Using ROC curves analyzing cardioembolic versus non-cardioembolic infarcts (atherothrombotic, lacunar and undetermined), we found that the best cut-off point of pro-BNP to predict cardioembolic stroke was 360 pg/mL (area under curve 0.921, sensitivity 87%, specificity 83%, *p* < 0.0001), of pro-ANP 2266.6 fmol/mL (area under curve 0.735, sensitivity 62%, specificity 70%, *p* < 0.0001) and of CK-MB 2.6 ng/mL (area under curve 0.731, sensitivity 62%, specificity 80%, *p* < 0.0001). In a logistic regression model, pro-BNP > 360 pg/mL (OR: 28.51, CI 95%: 5.90–136.75, *p* < 0.0001) was independently associated with higher risk of cardioembolic stroke, after adjustment for significant variables in univariate analysis (Table 2).

In a further analysis of undetermined infarcts, using the above criteria, 34 patients (41%) were reclassified as likely cardioembolic, 22 patients (27%) as likely atherothrombotic, and 26 patients (32%) remained

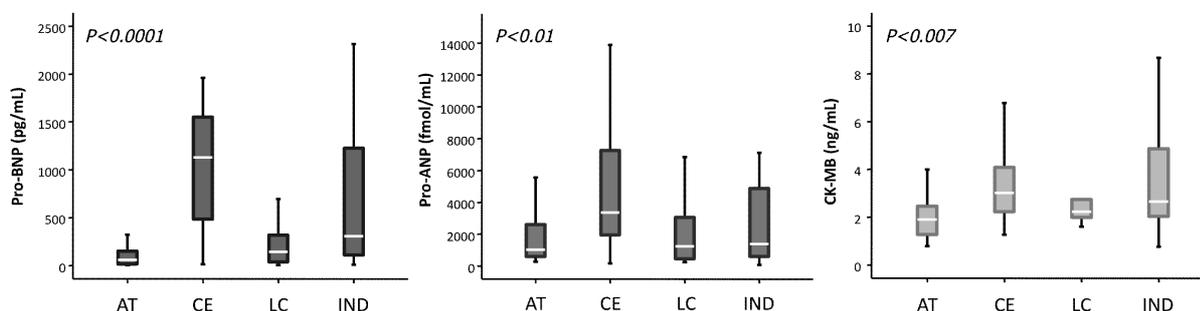


Fig. 1. Molecular markers values across the different etiological groups. AT: atherothrombotic; CE: cardioembolic; LC: lacunar; UND: undetermined.

Table 2

Logistic regression model, dependent variable cardioembolic stroke

	OR	CI 95%	p
Age	0.90	0.81–1.14	0.618
Sex, female	0.72	0.26–3.17	0.694
Diabetes	1.10	0.21–7.98	0.886
Coronary heart disease	2.74	0.51–15.46	0.129
Atrial fibrillation	20.63	4.24–100.91	< 0.0001
Temperature	1.13	0.86–26.40	0.308
Fibrinogen	1.00	0.94–1.13	0.166
Basal NIHSS	1.00	0.92–1.20	0.388
DWI volume	0.93	0.90–1.12	0.077
Stenosis > 50%	0.30	0.2–318.74	0.904
Intracranial stenosis	0.26	0.10–2.74	0.144
Pro BNP \geq 360	28.51	5.90–136.75	< 0.0001
Pro ANP \geq 2266.6	1.26	0.92–1.78	0.127
CK-MB \geq 2.6	3.3	1.1–10.1	0.032

as undetermined. Basal characteristics and biomarker serum levels of these subgroups of patients are shown in Table 3. In a logistic regression model in undetermined patients, analyzing likely cardioembolic versus non-likely cardioembolic (likely atherothrombotic and undetermined), only pro-BNP > 360 pg/mL (OR: 35.8, CI 95%: 5.68–225.16, $p < 0.0001$) was independently associated with likely cardioembolic stroke.

4. Discussion

This study shows that patients with cardioembolic stroke have higher levels of molecular markers of cardiac damage (pro-ANP, pro-BNP and CK-MB), in comparison to the other etiological subtypes of stroke. Pro-BNP was the most powerful molecular marker associated with cardioembolic stroke. Serum levels of pro-BNP > 360 pg/mL increased about 30 fold the probability of cardioembolic stroke in the whole group. Furthermore, pro-BNP levels were useful to reclassify undetermined strokes. Pro-BNP serum levels > 360 pg/mL among

patients with stroke of unknown etiology were found in 94.1% of those likely cardioembolic, whereas in none of those likely atherothrombotic.

BNP is a neurohormone that is synthesized and released primarily from the cardiac ventricles in response to increased wall tension [18,28], but it is also secreted by the brain, which is actually the organ where this substance was first identified [26]. Pro-BNP levels are increased in patients with acute stroke [32], but it is not well known if BNP is released by the ischemic brain or if this increase is due to previous of concurrent heart damage. Furthermore, the fact that BNP levels are higher in cardioembolic stroke independently of infarct volume, suggests that this increase may be related, at least in part, to a previous heart disease potentially associated with a cardiac source of embolism.

A recent study in patients with ischemic stroke found that increased pro-BNP levels are associated with electrocardiogram abnormalities suggestive of myocardial ischemia [12]. However, in our series we excluded patients with these abnormalities suggestive of myocardial ischemia in electrocardiogram. High levels of pro-BNP have also been associated with atrial abnormalities in patients with ischemic stroke, such as atrial dilatation, low flow velocity, spontaneous echocontrast or intraventricular thrombus, and atrial fibrillation [6]. Embolism of cardiac origin accounts for about 20% of ischemic strokes [22], and the majority of cardioembolic strokes are due to atrial fibrillation [3,14,15,29]. Paroxysmal atrial fibrillation is an underdiagnosed arrhythmia associated with an increased risk of ischemic stroke comparable to that of chronic atrial fibrillation [4,15]. Patients with paroxysmal atrial fibrillation show also higher levels of BNP [27], so these high levels in patients with stroke of undetermined origin might reflect the presence of paroxysmal atrial fibrillation or of any other atrial abnormality as potential cardioembolic source.

Table 3
Basal characteristics of undetermined infarcts reclassified, univariate analysis

	Likely atherothrombotic <i>n</i> = 22	Likely cardioembolic <i>n</i> = 34	Undetermined <i>n</i> = 26	<i>p</i>
Age, years	60.0 ± 14.3	73.0 ± 6.1	71.0 ± 9.5	< 0.0001
Female, %	27.3	47.1	30.8	0.245
History of hypertension, %	27.3	64.7	53.8	0.022
History of diabetes, %	18.2	17.6	15.4	0.961
Hypercholesterolemia, %	18.2	29.4	30.8	0.560
Smoker, %	45.5	5.9	15.4	0.001
Alcohol consumption > 40 g/day, %	27.3	0	0	0.001
Coronary heart disease, %	0	0	7.7	0.110
Atrial fibrillation, %	0	5.9	7.7	0.439
SBP, mm Hg	146.2 ± 28.1	150.0 ± 14.5	158.4 ± 12.9	0.442
DBP, mm Hg	82.9 ± 16.9	79.8 ± 13.3	77.1 ± 20.8	0.177
Body temperature, °C	36.4 ± 0.3	36.3 ± 0.3	36.1 ± 0.2	0.434
Glucose, mg/dL	122.9 ± 32.1	131.8 ± 70.2	141.3 ± 24.1	0.196
Fibrinogen, mg/dL	369.5 ± 86.2	371.5 ± 114.5	372.7 ± 77.5	0.995
Basal NIHSS	8 [5, 10]	14 [9, 16]	12 [5, 19]	0.004
DWI volume at admission, cc	10.9 [4.5, 41.6]	21.6 [6.0, 90.0]	20.7 [12.3, 86.4]	0.005
Carotid stenosis >50%, %	18.2	0	0	0.003
Carotid stenosis ≤50%, %	81.8	0	0	< 0.0001
Intracranial stenosis, %	18.2	11.8	0	0.093
Pro BNP, pg/mL	45.2 [15.1, 159.2]	1290.0 [871.6, 1692.2]	183.9 [121.8, 570.7]	< 0.0001
Pro-ANP, fmol/mL	513.3 [199.9, 1064.4]	2847.4 [1271.5, 6296.2]	1299.3 [848.3, 4392.5]	< 0.0001
CK-MB, ng/mL	2.5 [1.9, 4.3]	3.2 [2.3, 4.9]	3.6 [2.1, 4.9]	0.564
Pro-BNP ≥ 360 pg/mL, %	0	94.1	30.8	< 0.0001

SBP: systolic blood pressure, DBP: diastolic blood pressure, DWI: diffusion-weighted image, BNP: brain natriuretic peptide, ANP: atrial natriuretic peptide, CK-MB: creatin kinase-MB.

BNP manifest substantial biological variability [30] and multiple assays [2] exists for its determination. We have measured NT-proBNP by Elecsys 2010 (Roche), a method for measurement of pro-BNP clinically available, because several studies indicate that NT-proBNP testing has the same clinical utility as BNP [5,11,24]. Besides, NT-proBNP as measured by the Elecsys assay may be stored at -20°C for at least four months without a relevant loss of the immunoreactive analyte [17]. This is an important point to reduce the interassay coefficient of variance. Another important point is that the biologic half-life for BNP is 20 versus 70 minutes for NT-proBNP and may be the result of differences in the clearance rate of these peptides from blood [31]. These details together with the fact that the lower value of biological variability was found for NT-proBNP support the validity of the results obtained in the study and suggested that the NTproBNP has more of an “averaging” effect, whereas BNP is more sensitive to acute changes in the disease processes

This study has a number of limitations. CHADS₂ scale was designed to assess the embolic risk in patients with atrial fibrillation, but not in those with undetermined stroke. Few patients were undetermined by two causes, but in most of patients no atherothrombotic or embolic source was found. Only patients with

undetermined stroke were subjected to CHADS₂ and atherothrombotic risk scales, which could lead to bias, since these scales are not validated for the reclassification of undetermined stroke. The temporal profile of these molecular markers was not investigated in our study, and some studies found that pro-BNP levels decrease in the following days after stroke [32], so we cannot conclude if the increase of these molecular markers is the result of the ischemic lesion or reflects a previous cardiac damage. Other limitation is that we do not have information about previous treatment before admission that may affect pro-BNP levels.

In conclusion, we have found that serum levels of pro-BNP > 360 pg/mL within the first 24 hours from stroke onset may be useful to identify patients with an unknown cardiac source of cerebral embolism.

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