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Original Contribution

Contribution of routine cardiac biological markers to the etiological workup of ischemic stroke

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ABSTRACT

Background: Optimization of the detection of atrial fibrillation following stroke is mandatory. Unfortunately, access to long-term cardiac monitoring is limited in many centers. The aim of this study was to assess the potential usefulness of three routine biological markers, troponin, D-dimers and BNP, measured in acute stroke phase in the selection of patients at risk of cardio-embolic stroke.

Methods: Troponin, D-Dimers and BNP were measured within 48 h after admission for ischemic stroke in 634 patients. Stroke mechanism was defined at the 3 months follow-up visit using ASCOD classification using a standardized work-up. Association between clinical, radiological and biological markers and stroke mechanism was evaluated using logistic regression analyses.

Results: 159 patients (25.1% of total study population) had a cardiac mechanism. On multivariate analysis, admission initial stroke severity (OR 1.04, 95 CI% 1.004–1.07, $p < 0.05$) history of heart failure (OR 3.03, 95% CI 1.19–7.73, $p < 0.05$), ECG abnormalities and high BNP value (OR 4.34, 95% CI 2.59–7.29, $p < 0.05$) were associated with pure cardiac stroke mechanism.

Conclusion: High BNP value measured within 48 h after stroke admission is an independent predictor of cardiac stroke mechanism. Its measurement might be used to improve the selection of patients for whom further cardiologic investigations such as continuous long term ECG monitoring would be the most useful. BNP should be added to the standard admission-work-up for stroke patients.

1. Introduction

Risk of stroke recurrence after a first ischemic event is estimated around 10% in the first year and reaches 20 to 30% at five years [1]. Early recognition of stroke mechanism is a critical step to optimize secondary prevention. Indeed, among the wide sources of ischemic stroke, the identification of cardiac causes is of special interest because it directly leads to the introduction of anticoagulants [2]. Atrial fibrillation (AF) accounts for 50% of cardioembolic strokes, but could also be an underlying cause of 30% of embolic stroke of unknown sources [3,4]. Therefore the optimization of the detection of AF following stroke is mandatory. It is well known that increased duration of ECG recording is associated with higher rates of AF detection [5]. However the availability of external long term monitoring and implantable devices is still limited and cannot be performed to every stroke patient with unknown stroke mechanism, suggesting the need to identify a set of biomarkers that could improve the selection of patients that would benefit from these investigations.

Currently some heart rhythm characteristics (i.e. frequent premature beats) or cardiac morphologic parameters (i.e. left atrial dilation) are the most well known predictors [6]. In addition, three biomarkers, widely available in the clinical setting, showed promising results in this context: the Brain Natriuretic Peptid (BNP) and NT-proBNP [7] reflecting cardiac dysfunction, troponin [8,9], reflecting cardiac ischemia, and D-dimers [10], a marker of thrombosis. However most of these studies used advanced biochemical techniques to measure the levels of these biomarkers and did not address their value when measured in the context of a routine evaluation. The aim of this study was investigate the association between a "triple positivity" of this set of biomarkers and the presence of a cardiac source of stroke in order to determine their potential usefulness in the selection of patients requiring long-term cardiac monitoring.

2. Material and methods

2.1. Study population

We performed a retrospective monocentric study by gathering data from electronic medical records of patients who were admitted in our stroke unit from January 2016 to October 2016.

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Patients were eligible if they had had an ischemic stroke confirmed on brain imaging (CT or MRI), were part of the regional stroke observatory (ObA2) and had troponin, D-dimers and BNP levels available. Patients were excluded from the study if they had an alternative diagnosis to stroke (including TIA), if they had not benefited from at least 48 h telemetry in our unit, or if one or more biological data were missing among troponin, BNP and D-dimers levels. For every patient, demographical data (sex, age, NIHSS score at admission, pre-stroke and discharge Rankin score) and medical history (AF, diabetes, arterial hypertension, heart failure, stroke and vascular disease) was collected, as well as the CHA2DS2-VASC score [11], regardless of any history of AF and without taking into account the current stroke. Administration of intravenous thrombolysis or mechanical thrombectomy was documented.

2.2. Clinical protocol

Biomarkers samples were drawn within 48 h after admission (D-dimers levels had to be measured before intravenous thrombolysis if any). According to our lab, normal values were as follow: BNP <100 pg/mL (chemiluminescent immunoassay), troponin I <0,04 ng/mL (chemiluminescent immunoassay), D-dimers <500 ng/mL (ELISA). For patients over 50 years old, we calculated the normal limit value of D-dimers adjusted to age (<age × 10 in ng/mL) [12]. When biomarkers were collected at several time points, only the first one was considered in the analysis. For multivariate analysis, a global biological score was established by adding up the number of elevated biomarker levels, ranging from 0 to 3.

Each patient had a brain imaging (MRI or CT) to establish the diagnosis of stroke and its unique or multiples locations. Etiological workup included extra- and intracranial assessment of cerebral arteries using CT or MR angiography, ECG, at least 48 h telemetry in the intensive stroke care unit, 24 h-Holter-ECG, TTE and/or transesophageal echography) and laboratory testing including at least complete blood cell count, standard coagulation tests, serum electrolytes, assessment of liver and renal function, CRP, HbA1c and lipid profile). No internal or external continuous long term (>48 h) ECG monitoring was performed for these patients.

2.3. Stroke categorization

Stroke etiology categorization according to the ASCOD classification [13] was established at 3 months during a follow-up visit. If none or more than one of the 5 potential stroke mechanisms from the ASCOD classification were considered as a potential cause, stroke mechanism was considered as undetermined. Patients for which a cardiac pathology was the cause of stroke, thus ranked “C1”, were group 1. This group was compared to group 2, which included patients with another mechanism than cardiac pathology ranked “1” and those with none or more than one of the 5 mechanism in the classification ranked “1”.

2.4. Statistical analysis

Results from quantitative variables were presented using averages and standard deviations (SD) for age and NIHSS score, and with medians and extreme values for Rankin score and CHA2DS2-VASC score. Qualitative variables were described in frequency and proportions. Comparisons between groups 1 and 2 were done using Student's *t*-test or Fisher's exact test for parametric and non parametric variables. Distribution of variables CHA2DS2-VASC and Rankin score were compared between the 2 groups using ANOVA analysis.

We evaluated the clinical and paraclinical variables associated with a cardioembolic stroke mechanism by studying the association between these variables and groups 1 and 2 with a logistic regression model in a univariate analysis. Two models of multivariate analyses were built: model 1 included the main clinical parameters and each of the 3 biomarkers, model 2 included CHA2DS2-VASC and a global biological score for biomarkers ranging from 0 to 3. Variables with a $p < 0.2$ in the univariate analysis were included in a multivariate analysis. Variables with a $p > 0.2$ composing the CHA2DS2-VASC were entered in model 2. $p < 0.05$ was considered statistically significant. All statistical analysis were done using IBM© SPSS© Statistics Base 22.0.

3. Results

During the study period, 857 potentially eligible patients were identified. 223 patients were excluded because of incomplete biological data. 634 patients were included, 159 of them (25.1% of total study population) were part of Group 1 (C1 mechanism). Fig. 1 represents the patient flow-chart.

3.1. Group classification

In group 1, AF was the most common cause (135 patients, 84.9%). AF was known before the ischemic event for 51.8% of the population, and discovered in the stroke unit for 55 patients, either on admission ECG ($n = 24$), telemetry ($n = 30$) or in-hospital 24 h-Holter ECG ($n = 1$ among 10 recordings). Diagnosis of AF was made between discharge from the stroke unit and the 3 months follow-up visit for 10 patients, based on the results of 24 h-Holter ECG.

In group 2, 219 patients (46.3% of group 2) had another mechanism than cardioembolism ranked “1” (atherosclerosis, small-vessel disease, dissection, other causes) at the 3 months follow-up visit. For 236 patients (49.7% of group 2), stroke mechanism was considered undetermined either because of several mechanisms ranked “1” (20 patients with AF, 4.2% of group 2) or because none of the mechanism ranked “1”.

3.2. Comparisons between group 1 and 2

Comparisons between group 1 and 2 are represented in Table 1.

3.2.1. Demographical and clinical data

Groups 1 and 2 did not differ significantly in terms of sex ratio, with a male predominance in both groups (respectively 56% and 62.3%). Age was significantly higher in group 1 (75.3 y.o vs. 67.1, $p < 0.05$). Pre-stroke Rankin score did not differ between the 2 groups. Patients from group 1 had significantly more severe stroke (mean admission NIHSS 7.8 vs. 4.5) and worse outcome at 3 months.

3.2.2. Cardiovascular comorbidity and CHA2DS2-VASC

CHA2DS2-VASC score was significantly higher in group 1, due to an over-representation of 3 items: history of hypertension (67.9% vs. 56.4%, $p < 0.05$), heart failure (10.1% vs. 2.1%, $p < 0.05$) and vascular disease (22.0% vs. 12.4%, $p < 0.05$).

3.2.3. Therapeutic intervention

There was no difference between the 2 groups in term of intravenous thrombolysis. However, patients in group 1 were more frequently treated by mechanical thrombectomy (28.3% vs. 11.2%, $p < 0.05$).

3.2.4. Paraclinical results

Biomarkers levels (BNP, troponin I and D-dimers) were significantly higher in group 1, with a frequency of increase being the most important for BNP (BNP 83.0% vs. 39.2%, D-dimers 65.4% vs. 44.22%, troponin I 24.5% vs. 8.6%, $p < 0.05$ for the 3 parameters). Frequency of multifocal stroke did not differ between the groups.

3.3. Parameters associated with a cardioembolic mechanism (C1)

Results from univariate and multivariate analysis are presented in Table 2. Among clinical data recorded at admission only initial stroke

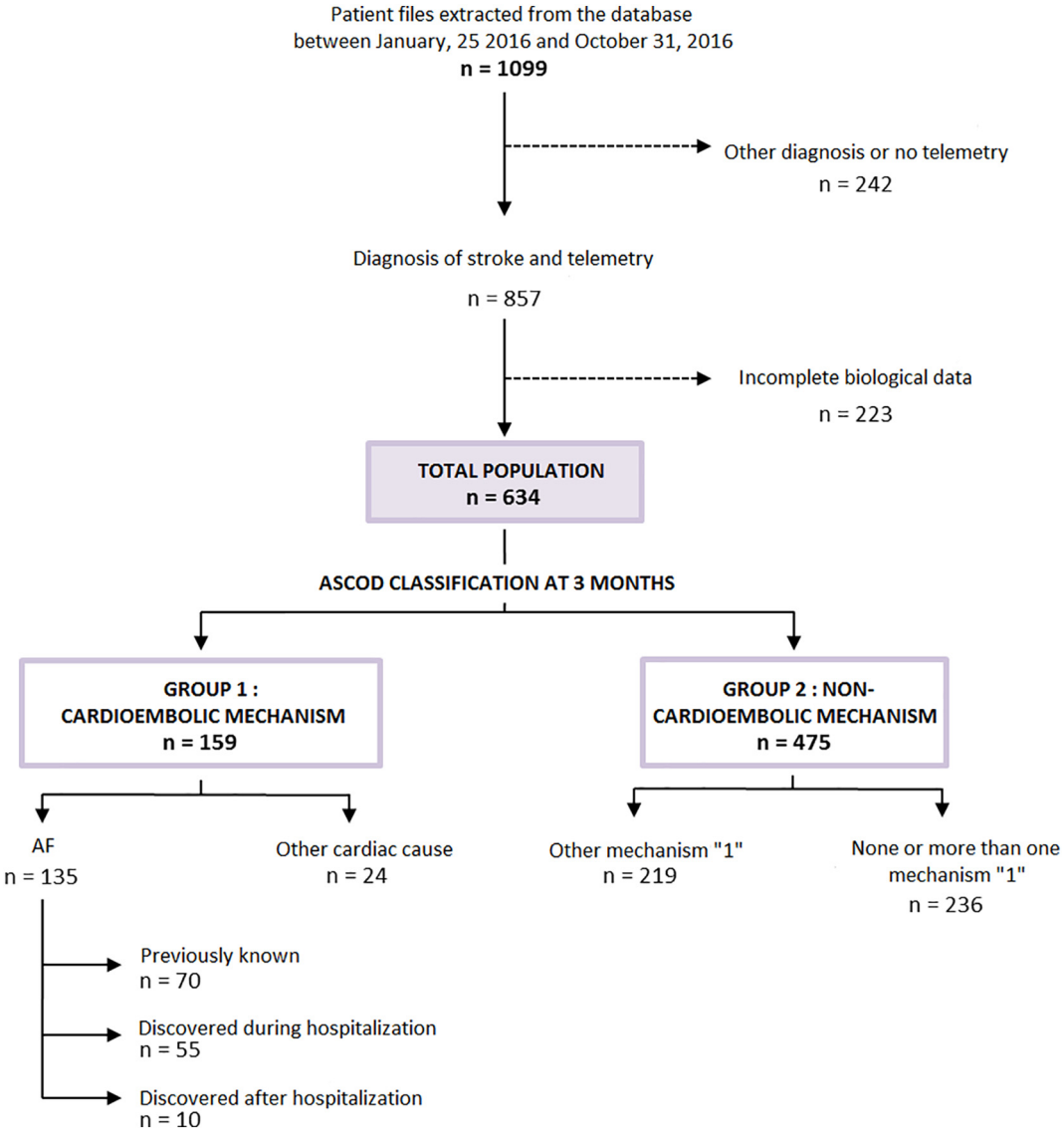

Fig. 1. Patient flow chart.

severity (OR 1.04, 95 CI% 1.004–1.07, $p < 0.05$) and a history of heart failure (OR 3.03, 95% CI 1.19–7.73, $p < 0.05$) were associated with a pure C1 mechanism at 3 months. ECG abnormalities were also significantly associated with a C1 mechanism in both models while multiple stroke location was not. Among the 3 biological markers, BNP was the only one that reached statistical significance in the multivariate analysis in model 1 (OR 4.34, 95% CI 2.59–7,29, $p < 0.05$). When the sum of the 3 biomarkers was studied in model 2, it was associated with a cardioembolic mechanism (OR 2.37, 95% CI 1.86–3.02, $p < 0.05$). Sensitivity and specificity for each biological marker elevation were respectively: 83.0% and 60.8% for BNP, 24.5% and 91.4% for troponin, and 65.4% and 55.7% for D-dimers.

Two additional multivariate analyses were carried out (data not shown): the first studied markers associated to patients ranked C1 only due to AF (model 3), the second studied markers associated with AF while excluding patients whose AF was already known before the ischemic stroke (model 4). In model 3, BNP level and ECG abnormalities were the only parameters associated to AF, with BNP remaining the most significantly (respectively OR 5.65, 95% CI 3.25–9.81, $p < 0.05$ and OR 1.59, 95% CI 1.17–2.17, $p < 0.05$). In model 4, BNP was the only parameter associated with newly identified AF (OR 4.70, 95% CI 2.12–10.42, $p < 0.05$).

4. Discussion

The main results of this study are the following: i) Increased levels of BNP, troponin and D-dimers early after stroke are significantly associated with cardiac sources of stroke, mainly AF; ii) Increased BNP is the most sensitive biomarker compared to troponin and D-dimers and iii) Biological markers are more associated with cardiac stroke mechanism than clinical and radiological markers represented by the CHADS-VASC score and multifocal stroke distribution.

Several studies have investigated the association between biological markers such as BNP, troponin or D-dimers and the underlying stroke mechanism [10,14-17]. However few of them have assessed the predictive value of a combination of these measures that encompass different pathophysiological processes such as cardiac insufficiency, ischemic heart disease and hypercoagulability. Our results confirm the strong association between a high global biological score of the measured biomarkers and the probability of a cardiac source of stroke (OR 2.37. 95% CI 1.86–3.02) but do not demonstrate a better association than BNP alone (OR 4.34. 95% CI 2.59–7.29. $p < 0.05$) which do not support the hypothesis that the measure of these 3 markers might improve the early identification of patients with a probable cardiac stroke mechanism in routine clinical practice. BNP is mainly synthesized by cardiomyocytes

Table 1
Characteristics of stroke patients according to stroke mechanism.

	Total population	Group 1 (C1 patients)	Group 2 (non-C1 patients)	Comparison between groups 1 and 2
	n = 634	n = 159	n = 475	p
Demographical and clinical data				
Female (%)	249 (39.3)	70 (44.0)	179 (37.7)	0.15
Age (SD)	69.2 (16.2)	75.3 (12.2)	67.1 (16.9)	<**0.05**
Pre-stroke mRS	0 (0–5)	0 (0–5)	0 (0–4)	0.40
Admission NIHSS (SD)	5.4 (6.2)	7.8 (7.0)	4.5 (5.7)	<**0.05**
mRS at discharge	1 (0–6)	1 (0–6)	1 (0–6)	<**0.05**
Cardiovascular comorbidities				
Diabetes (%)	161 (25.4)	42 (26.4)	119 (25.1)	0.73
Hypertension (%)	376 (59.3)	108 (67.9)	268 (56.4)	<**0.05**
Cardiac insufficiency (%)	26 (4.1)	16 (10.1)	10 (2.1)	<**0.05**
Cerebral ischemia (%)	87 (13.7)	22 (13.8)	65 (13.7)	0.96
Vascular disease (%)	94 (15.2)	35 (22.0)	59 (12.4)	<**0.05**
Atrial fibrillation (%)	90 (14.2)	70 (44.0)	20 (4.2)	<**0.05**
CHA2DS2-VASC	3 (0–7)	3 (0–7)	3 (0–7)	<**0.05**
Therapeutic				
IV thrombolysis (%)	125 (19.7)	35 (22.0)	90 (18.9)	0.40
Mechanical thrombectomy (%)	98 (15.5)	45 (28.3)	53 (11.2)	<**0.05**
Imaging results				
Multifocal stroke (%)	113 (17.8)	30 (18.9)	83 (17.5)	0.69
ECG results				
Normal	500 (80.4)	85 (53.5)	415 (87.4)	<**0.05**
Atrial fibrillation	71 (11.4)	56 (35.2)	15 (3.2)	
Other abnormalities	51 (8.2)	14 (8.8)	37 (7.79)	
Biological results				
Increased troponin I (%)	80 (12.6)	39 (24.5)	41 (8.6)	<**0.05**
Increased D-dimers (%)	314 (49.5)	104 (65.4)	210 (44.2)	<**0.05**
Increased BNP (%)	318 (50.2)	132 (83.0)	186 (39.2)	<**0.05**

Statistically significant p value (<0.05) appears in bold.

from the ventricles and is increased in most cases of cardiac dysfunction contributing to AF. Our results are in accordance with several previous studies and meta-analysis that have established an association between increased BNP or NT-proBNP and cardioembolic stroke [18-21]. However, results were better for NT-proBNP [22] which is a marker not available in every center for clinical practice at a low cost. Herein, our results suggest that a measurement of BNP as it is easily obtained in daily practice could offer an interesting opportunity to identify patients with a high probability of cardiac stroke mechanism. Although our results confirmed the well-known association between cardio-embolic mechanism and more severe stroke [7], we failed to identify a significant association with the CHADS-VASC status while it has been reported [23]. This result might be explained by the predominant role played by heart failure which is highly correlated to increased BNP levels [24]. However, we also found an independent association between higher BNP at admission and the identification of AF during follow-up suggesting that this marker is not the sole consequence of cardiac insufficiency but could be considered as an indicator of a myocardial dysfunction increasing the risk of AF [25]. This hypothesis is also supported by the association observed between any ECG abnormalities and C1 stroke mechanism. The combination of clinical, biological and abnormal cardiac rhythm abnormalities has already been reported to improve the detection of patients with a high probability of cardiac stroke mechanism [26] and is reinforced by the present results. Conversely, stroke location was a poor indicator, in line with previous results [27].

Results of this study have to be interpreted cautiously due to several limitations. First a high number of patients had neither TEE nor long term ECG monitoring which might have led to overestimate the proportion of patients with cryptogenic stroke. Second, echocardiographic parameters were not included in the model while several studies have demonstrated a clear association between morphological abnormalities such as left atrial dilation and a higher risk of AF, therefore improving predictive models when added to clinical, biological and heart rhythm abnormalities [6]. However access to TEE is still limited at many centers in the early stroke phase and our results suggest that a combination of severe stroke, high BNP level and abnormal ECG can help to identify a subpopulation of stroke patients with a high probability of cardiac stroke sources. Such parameters might be used to improve the selection of patients for whom further cardiologic investigations such as continuous long term ECG monitoring would be the most useful. The recent interruption of the Navigate Trial for futility reinforces the need to improve our ability to identify patients with cardiac stroke sources in the context of limited access to advanced cardiac investigation in our daily practice.

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Table 2
Acute stroke parameters associated with diagnosis of cardioembolic mechanism at 3 months (C1).

Clinical and paraclinical data	Univariate analysis			Multivariate analysis model 1			Multivariate analysis model 2	
	OR	95% CI	p	OR	95% CI	p	OR	95% CI
Age	1.04	1.03–1.06	<**0.05**	1.02	0.99–1.03	0.06		
Sex	1.30	0.90–1.87	0.16	1.05	0.68–1.62	0.83		
Admission NIHSS	1.08	1.05–1.11	<**0.05**	1.03	1.00–1.06	0.06	1.04	1.004–1.07
Diabetes	1.07	0.71–1.62	0.73	1.06	0.65–1.72	0.82		
Hypertension	1.64	1.12–2.39	<**0.05**	1.01	0.63–1.63	0.95		
Heart failure	5.20	2.31–11.72	<**0.05**	3.03	1.19–7.73	<**0.05**		
Cerebral ischemia	1.01	0.78–1.31	0.96	0.95	0.69–1.30	0.76		
Vascular disease	1.96	1.23–3.12	<**0.05**	0.86	0.48–1.51	0.59		
CHA2DS2-VASC	1.12	1.004–1.24	<**0.05**				0.96	0.85–1.09
Multifocal stroke	1.10	0.69–1.74	0.69	0.59	0.34–1.04	0.07	0.61	0.36–1.05
ECG	2.30	1.75–3.03	<**0.05**	1.58	1.15–2.16	<**0.05**	1.80	1.33–2.41
Elevated troponin I	3.44	2.12–5.57	<**0.05**	1.76	0.99–3.14	0.06		
Elevated D-dimers	2.38	1.64–3.45	<**0.05**	1.42	0.91–2.23	0.12		
Elevated BNP	7.60	4.83–11.95	<**0.05**	4.34	2.59–7.29	<**0.05**		
Global biological score							2.37	1.86–3.02

Statistically significant p value (<0.05) appears in bold.

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