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Biomarkers for the identification of atrial fibrillation in ischemic stroke: Atrial Natriuretic Peptide versus N-terminal-pro Brain Natriuretic Peptide

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Resumo

Um terço dos acidentes vasculares cerebrais (AVC) isquémicos têm etiologia indeterminada pela classificação TOAST. Parte deve-se a episódios paroxísticos de fibrilhação auricular (FA). Vários estudos mostraram a utilidade do N-terminal do péptido natriurético cerebral (NT-proBNP) na identificação de AVC cardioembólico associado a FA. Porém, o péptido atrial natriurético (ANP), produzido nas aurículas, poderá ter maior acuidade que o NT-proBNP no diagnóstico de FA, sendo esta uma arritmia de origem atrial. O objetivo deste trabalho foi determinar qual dos biomarcadores, ANP ou NT-proBNP, tem maior acuidade para diagnosticar FA em doentes com AVC isquémico.

Realizou-se um estudo observacional utilizando uma coorte de doentes com amostras biológicas guardadas no biobanco do Instituto de Medicina Molecular, internados de agosto de 2012 a outubro de 2013 na Unidade de AVC do Hospital de Santa Maria. Critérios de inclusão: AVC isquémico agudo ou acidente isquémico transitório (AIT); consentimento para recolha e análise de amostras de sangue e sua disponibilidade no biobanco do IMM. Critérios de exclusão: TFG<30mL/min; colheita amostral >72 horas após o início de sintomas ou quantidade insuficiente; etiologia indeterminada por duas ou mais causas possíveis. Determinou-se a etiologia do AVC pela classificação TOAST. A análise estatística incluiu determinação e comparação de curvas ROC.

Incluíram-se 198 doentes, 61.6% homens, com idade mediana 65 anos. As curvas ROC para o diagnóstico de eventos cardioembólicos com FA versus não cardioembólicos obtiveram as *AUC*: NT-proBNP 0.82 (IC 95% 0.74-0.89) e ANP 0.69 (IC 95% 0.60-0.78). No diagnóstico de cardioembólicos com FA versus indeterminados: NT-proBNP 0.83 (IC 95% 0.75-0.91) e ANP 0.68 (IC 95% 0.57-0.79).

NT-proBNP mostrou maior acuidade para diagnosticar FA que o ANP, o que pode dever-se à semi-vida plasmática do ANP ser inferior à do NT-proBNP. Concluiu-se que o NT-proBNP deverá permanecer o biomarcador de eleição para auxiliar o diagnóstico de FA no AVC isquémico.

Palavras-chave: Acidente vascular cerebral; Etiologia; Biomarcadores; Fibrilhação auricular; Péptidos Natriuréticos.

Abstract

One-third of ischemic stroke's etiology is undetermined according to the TOAST classification. A fraction is due to paroxysmal atrial fibrillation (AF) events. Many studies demonstrated the utility of N-terminal pro-brain natriuretic peptide (NT-proBNP) for identifying cardioembolic stroke associated with AF. However, atrial natriuretic peptide (ANP), synthesized in the atria, could have higher acuity than NT-proBNP for diagnosing AF, an atrium originated arrhythmia. The objective of this study was to determine which biomarker, ANP or NT-proBNP, has higher diagnostic accuracy for AF in patients with ischemic stroke.

An observational study was carried out, with a cohort of patients whose biological samples were stored in the biobank of Instituto de Medicina Molecular and who were admitted to the stroke unit of Hospital de Santa Maria between August of 2012 and October of 2013. Inclusion criteria: acute ischemic stroke or transient ischemic attack (TIA); consent to collecting and analyzing blood samples and their availability in the biobank of IMM. Exclusion criteria: GFR<30ml/min; samples collected >72 hours after the start of symptoms or insufficient amount; undetermined etiology due to two or more possible causes. Stroke etiology was determined with the TOAST classification. Statistical analysis included determination and comparison of ROC curves.

A sample of 198 patients was included, with median age of 65 years and 61.6% of men. The ROC curves for cardioembolic with AF versus noncardioembolic stroke had the following AUC: NT-proBNP 0.82 (95% CI 0.74-0.89) and ANP 0.69 (95% CI 0.60-0.78). For diagnosing cardioembolic with AF versus undetermined stroke: NT-proBNP 0.83 (95% CI 0.75-0.91) and ANP 0.68 (95% CI 0.57-0.79).

NT-proBNP presented a higher accuracy than ANP for diagnosing AF. This can be explained by the fact that ANP's plasma half-life is shorter than NT-proBNP's. In conclusion, NT-proBNP should remain the biomarker of choice for diagnosing AF in ischemic stroke.

Keywords: Stroke; Etiology; Biomarkers; Atrial Fibrillation; Natriuretic Peptides.

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Abbreviation Dictionary

ACA – anterior cerebral artery

ACEI – angiotensin-converting-enzyme inhibitors

AF – atrial fibrillation

ANP – atrial natriuretic peptide

ARB – angiotensin II receptor blockers

AUC – area under the curve

BNP – b-type natriuretic peptide

BSA – body surface area

CI – confidence interval

CKD-EPI – chronic kidney disease epidemiology collaboration

CT – computerized tomography

ECG – eletrocardiogram

ICA – internal carotid artery

IQR – interquartile range

IMM – Instituto de Medicina Molecular

MCA – middle cerebral artery

MRI – magnetic resonance imaging

MR-proANP – mid-regional pro-brain natriuretic peptide

NOAC – novel oral anticoagulant

NIHSS – National Institutes of Health stroke scale

NT-proBNP – n-terminal pro-brain natriuretic peptide

pAF – paroxysmal atrial fibrillation

PCA – posterior cerebral artery

ROC curve – receiver operating characteristic curve

TIA – transient ischemic attack

TOAST - Trial of Org 10172 in Acute Stroke Treatment

Introduction

The evaluation of a patient with stroke includes, among other actions, the study of stroke etiology. The importance of this investigation lies in the fact that different etiologies condition distinctive approaches for the prevention of recurrent events, and different prognosis (Adams et al., 1993).

In this context, in 1993, the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification was published, dividing ischemic strokes into five subtypes according to their etiology (Adams et al., 1993). The integration of clinical data and data from imaging and laboratory diagnostic tests allows the attribution of a "probable" or "possible" etiological subtype, from the following: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology and stroke of undetermined etiology (Adams et al., 1993).

Most ischemic strokes fall into one of the first three categories (Kolominskt-Rabas et al., 2001; Murat Sumer & Erturk, 2002). However, in about one third of cases, the cause of stroke remains undetermined even after an extensive investigation (Kolominskt-Rabas et al., 2001; Murat Sumer & Erturk, 2002).

According to the TOAST classification, stroke etiology is defined as undetermined after an extensive evaluation from which there are no conclusive results (in about 20% of the events), when the evaluation is incomplete (in about 5% of all strokes) or when two or more possible causes are identified and the final etiology cannot be determined (in about 10% of the cases) (Adams et al., 1993; Nam et al., 2012). Recently, a subtype of ischemic stroke with undetermined etiology was defined, the embolic strokes of undetermined source (ESUS) (Hart et al., 2014). This is a subgroup within the cryptogenic strokes, in which the etiological investigation allows the exclusion of major risk causes of cardioembolic stroke, occlusive atherosclerosis, lacunar strokes and other specific causes of stroke (Hart et al., 2014).

Other classifications have been developed throughout the years, such as the Causative Classification of Stroke System (CCS) and A-S-C-O Classification (Marnane et al., 2010). These assign a smaller percentage of strokes to the subgroup of undetermined etiologies comparatively to the TOAST classification (Marnane et al., 2010).

The importance of this stroke subtype lies in its significant mortality and morbidity, mainly when it results from an incomplete evaluation (Murat Sumer & Erturk, 2002; Nam et al., 2012), and recurrence rate (about 9% at 6 months and 33% at five years) (Murat Sumer & Erturk, 2002; Petty et al, 2000). Thus, the investigation of situations that determine a stroke of undetermined etiology is an area of extreme relevance in today's clinical practice, in order to adopt appropriate therapeutic strategies for secondary prevention.

Many situations can potentially originate a cryptogenic stroke, such as paroxysmal atrial fibrillation (pAF), transient hypercoagulability states, vasospasm, changes in cerebral autoregulation, hemodynamic mechanisms, rupture of vulnerable plaques and *in situ* thrombotic occlusion. All this situations can be challenging to diagnose (Fonseca & Ferro, 2015). From the enumerated etiologies, the episodes of pAF stand out. AF is defined by a rhythm documentation with irregular RR intervals and no distinct P waves, lasting at least 30 seconds (Kirchhof et al., 2016). Paroxysmal episodes of AF have a spontaneous resolution in under seven days, most frequently in less than 48 hours, or are converted in the first seven days (Hu, Stevenson & Lilly, 2011; Kirchhof et al., 2016). Episodes of atrial fibrillation with a duration of at least 30 seconds were found in 16% of patients with cryptogenic strokes or TIA undergoing prolonged cardiac monitoring and showed a high recurrence rate (Gladstone et al., 2014).

Several methods for diagnosing AF in patients with strokes of undetermined etiology have been studied. The methods classically used for the diagnosis of AF in patients with ischemic stroke include a standard 12-lead electrocardiogram, continuous ECG monitoring during the first 48 to 72 hours after the event and a 24-hour Holter (Fonseca & Ferro, 2015). However, methods of prolonged cardiac monitoring, such as 30-day event-triggered recorders and implantable loop recorders, have been shown to have a higher detection rate of these transient arrhythmias than the conventional methods (Dahal et al., 2016; Rabinstein, 2014; Tsivgoulis et al., 2019). They also determine a higher rate of anticoagulant therapy initiation during follow-up, and subsequent lower risk of recurrent stroke (Tsivgoulis et al., 2019). Nevertheless, the sensitivity of most of these methods for the identification of AF is relatively low (Thomas & Lerman, 2011). This limitation led to a search for tests with higher

sensitivity and specificity for the identification of AF in patients with stroke of undetermined etiology.

There has been interest in the potential role of biomarkers for the investigation of stroke etiology (Kim, Moon & Bang, 2013). In the future, biomarkers may be suitable for screening high-risk subjects, providing a rapid stroke diagnosis, detection of possible stroke mechanisms, predicting drug response and outcomes and as surrogate endpoints in clinical trials (Kim, e al., 2013).

Some of the biomarkers that may possibly be useful in this context are the atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). These peptides are synthesized as pro-hormones, and while ANP remains stored in granules, BNP's synthesis and secretion occurs in bursts (Daniels & Maisel, 2007; De Lemos, McGuire & Drazner, 2003). Upon the stimulus for their secretion, the stretch of myocytes secondary to pressure or volume overload, ANP is released from granules into the circulation while BNP's gene expression increases (De Lemos et al., 2003). At this time, the pro-hormone is cleaved in an N-terminal inactive segment (N-terminal ANP and N-terminal BNP) and in an active hormone (ANP and BNP), which are released into the circulation (De Lemos et al., 2003). ANP is mostly released by the atrial tissue, while BNP reflects the tension in the ventricular walls, but both can be secreted by the two types of cardiac chambers in pathological situations (Yasue et al., 1994).

Many studies have shown a correlation between these biomarkers and the presence of AF and a cardioembolic stroke etiology (Bai et al., 2018; Berntsson et al., 2014; Fonseca et al., 2011; Llombart et al., 2015; Shiroto et al., 2017). In patients with an undetermined stroke etiology, BNP and NT-proBNP could be potentially useful, for example, to identify patients who would benefit the most from more prolonged heart monitoring to identify pAF (Llombart et al., 2015; Wachter et al., 2012; Wasser et al., 2020).

Therefore, since ANP is preferably produced by the atria, and AF is an arrhythmia with origin in these chambers, we aimed to determine if this natriuretic peptide had a higher sensitivity and specificity than BNP/NT-proBNP to identify AF in patients with ischemic stroke. Thus, the objective of this study is to compare the biomarkers ANP and NT-proBNP in order to determine which one has a higher accuracy for the diagnosis of AF in patients with ischemic stroke.

Material and Methods

Study type

This was an observational, retrospective cohort study.

Population

The population in this study consisted of a sample of patients consecutively admitted to the Stroke Unit of Hospital de Santa Maria between August of 2012 and October of 2013 with an acute ischemic stroke or transient ischemic attack (TIA).

Inclusion and exclusion criteria

In order to be included in the study, patients needed to have a diagnosis of acute ischemic stroke, defined by WHO's criteria (World Health Organization, 2002), and with simultaneous evidence of an ischemic lesion in the brain CT or brain MRI, or a diagnosis of TIA, defined as a temporary episode of focal neurologic deficits with rapid onset and resolution in less than a day, without persistent neurologic deficits (Advisory Council for the National Institute of Neurological Diseases and Blindness, 1975). As inclusion criteria there was also a previous informed consent to the collection and analysis of blood samples, and the confirmation of their availability in the biobank of the Instituto de Medicina Molecular (IMM).

Exclusion criteria were renal failure, defined as a glomerular filtration rate estimated by CKD-EPI's equation of less than 30mL/min, blood samples collected more than 72 hours after the start of the event, samples with insufficient amount for analysis and stroke with undetermined etiology due to two or more possible etiologies.

Sample size calculation

Based on the article by Fonseca et al. (2014), in which the sensitivity and specificity of the biomarker NT-proBNP for the diagnosis of pAF in patients with cryptogenic strokes were determined, it was decided that the sample size necessary to detect a significant difference between both biomarkers should be equal or greater than the one used in said study, which was of 264 patients.

Clinical protocol

Blood samples were collected from a peripheral vein during the first 72 hours after stroke or TIA onset and then stored in the stroke collection of the Biobank of the IMM. Later, in 2015, the samples were taken to a certified external laboratory. There, levels of NT-proBNP were measured by an electrochemiluminescence essay using the Elecsys 2010 immunoassay analyzer (Roche Diagnostics, Mannheim, Germany). ANP levels were measured by an electrochemiluminescence enzyme immunoassay.

A database was constructed with information from the clinical files of the patients and completed with data from the discharge notes and exam reports.

Collected information included:

- demographic characterization of the population, namely patients' age, sex, weight, and height;
- risk factors for stroke, such as arterial hypertension, diabetes *mellitus*, dyslipidemia, and smoking habits;
- personal background, such as history of a previous stroke, diagnosis of coronary disease, heart failure and previous AF diagnosis (and its subtype);
- drug history, in particular, drugs that could interfere with the levels of the biomarkers, like angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers and diuretics.

Stroke severity was evaluated at admission using the National Institutes of Health Stroke Scale (NIHSS) (Lyden et al., 1994). Patients were reevaluated using the same scale at hospital discharge. TOAST classification was used to establish stroke etiology (Adams et al., 1993). The modified Rankin scale was applied at discharge in order to determine functional outcome (van Swieten et al, 1988).

Data collected for the etiological study included:

- laboratory tests, in particular: blood count, renal function, coagulation studies, blood glucose and lipid profile;
- imaging as brain CT and brain MRI, in order to determine which was the affected territory;
- transcranial, carotid and vertebral Dopplers, transthoracic and/or transesophageal echocardiograms, electrocardiogram and 24-hour Holter.

The following parameters from the echocardiographic exams (transthoracic and/or transesophagic) were registered: presence of left atrial dilation (defined as left atrial volume/BSA > 34 mL/m^2 (Lang et al., 2015); presence of thrombi in the left atrium or atrial appendage; presence of a patent foramen ovale (associated or not with a interatrial septal aneurysm); presence of aortic plaques; left ventricle fractional shortening; fulfillment of left ventricular hypertrophy criteria (thickness of the interventricular septum or of the posterior wall of the ventricle > 0,9 cm for women and > 1,0 cm for men; LV mass/BSA > 95 g/m^2 for women and > 115 g/m^2 for men with linear methods or > 88 g/m^2 for women and > 102 g/m^2 for men with 2D methods) (Lang et al., 2015); left ventricle dilation (LV end-diastolic volume/BSA > 61 mL/m^2 for women and > 74 mL/m^2 for men or end-systolic volume/BSA > 24 mL/m^2 for women and > 31 mL/m^2 for men) (Lang et al., 2015); global systolic function (considered abnormal when the ejection fraction was inferior to 54% for women and 52% for men) (Lang et al., 2015); presence of diastolic dysfunction (when more than two of these criteria were met: average ratio E/e' > 14; annular e' velocity: septal e' < 7 cm/sec, e' lateral < 10 cm/sec; left atrial volume index > 34 mL/m^2; and peak tricuspid regurgitation velocity > 2,8 m/sec) (Nagueh et al., 2016); and segmental kinetic changes (segments of hypokinesia, akinesia or dyskinesia) (Lang et al., 2015).

AF was defined as a period of arrhythmic electrical activity with a duration of, at least, 30 continuous seconds, during which no P waves were registered (Kirchhof et al., 2016). Paroxysmal AF was defined as episodes with the characteristics previously described and a spontaneous resolution in seven or fewer days (Kirchhof et al., 2016).

Statistical analysis

Initially, a descriptive analysis was carried out, for demographic data, risk factors for stroke, personal history and therapeutics. Normality was tested using histograms and a one-sample Kolmogorov-Smirnov test. For numeric variables, measures of central tendency (such as mean or median) and measures of dispersion (such as standard deviation or interquartile range) were used if the variables had a normal distribution or not, respectively. For qualitative variables, frequencies and percentages were used.

Then, for comparison between groups, parametric tests (such as the one-sample t-test) and nonparametric tests (Mann-Whitney test, chi-square, and Fisher's exact test) were used as appropriate.

We performed five comparisons. First, patients were divided in two groups: cardioembolic stroke and noncardioembolic stroke, and these were compared. Next, we selected patients with the diagnosis of AF from the cardioembolic stroke group, considering those who had a previous diagnosis of AF and those in which the arrhythmia was identified in the ECG or 24-hour Holter performed during the etiological investigation. These were compared with the noncardioembolic group. Then, patients with a stroke of undetermined etiology were compared to the patients of the cardioembolic groups. Finally, we compared patients with cardioembolic stroke to those with stroke of other etiologies (large artery stenosis, small-vessel occlusion and other determined etiologies).

In order to define the diagnostic accuracy of ANP and NT-proBNP, ROC (receiver operating characteristic) curves were constructed, and the AUC (area under the curve) were determined. The comparison groups described above were used. A comparison between the ROC curves of each biomarker was also carried out using the method of DeLong, DeLong and Clarke-Pearson (1988).

Statistical significance was considered for a p-value under 0.05. Statistical analysis was carried out using IBM SPSS Statistics (version 24) and MedCalc Statistical Software (version 19.7.2).

Authorizations

The patients that took part in this study, or a family member or legal representative, signed an informed consent and all of their data is confidential. The project was approved by the Ethics Committee of the Hospital de Santa Maria and the biobank.

Results

1. Demographic Characterization

There were 209 patients initially included in the study, 6 of which were excluded due to a GFR < 30mL/min estimated by CKD-EPI equation using the MDCalc calculator, and 5 were excluded for having an undetermined etiology due to two or more possible etiologies. This resulted in a final sample of 198 patients (Fig. 1).

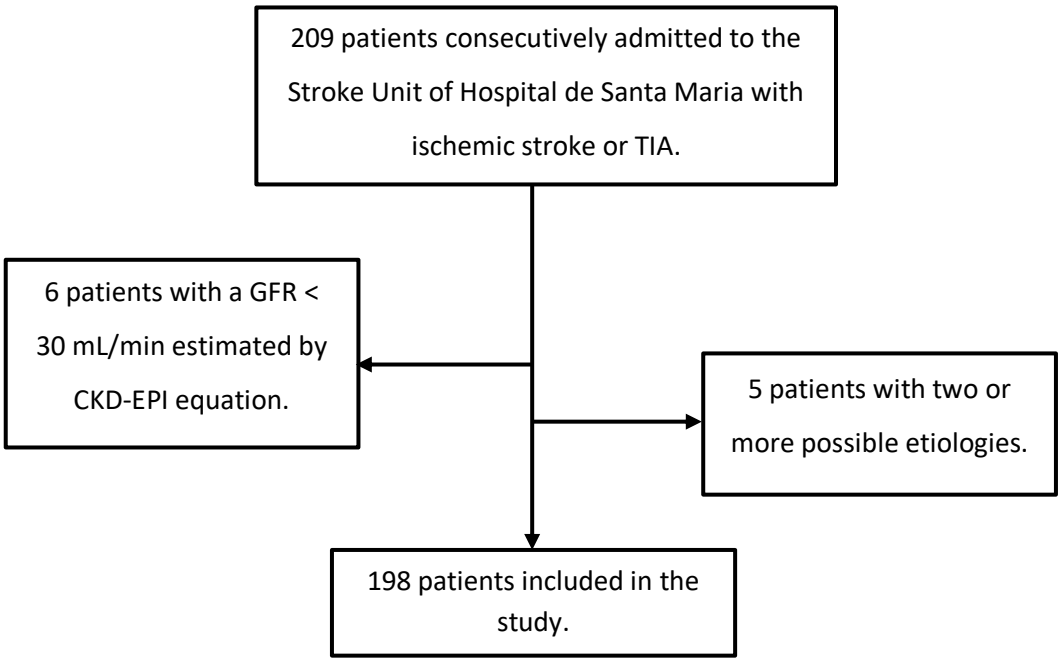

Figure 1. *Flowchart* of the patients included in the study.

As shown in Table 1, 61,6% of the patients included were male, with a median of 65 years of age (IQR 20,3). In terms of cardiovascular risk factors, the most frequent was arterial hypertension (123 (62,1%)), followed by dyslipidemia (98 (49,5%)). Fourteen patients (7,1%) had a previous diagnosis of AF and 42 (21,2%) had had a previous stroke. One hundred and fifty-eight events (79,8%) were strokes and the remaining were TIA.

After the establishment of stroke etiology according to the TOAST classification, 37 (18,7%) were due to large artery occlusion, 10 (5,1%) to small-vessel occlusion, 84 (42,4%) were cardioembolic, of associated which 41 (20,7%) with AF, 55 (27,8%) had an undetermined etiology, and 12 (6,0%) had other determined etiology, such as

carotid and vertebral artery dissection. Other cardioembolic stroke etiologies besides AF were patent foramen ovale, dilated cardiomyopathy, ventricular wall hypokinesis, rheumatic valvulopathy, sick sinus syndrome, infective endocarditis and to mechanical valve prothesis.

The most frequently affected territory was the territory of the medial cerebral artery (129 (65,2%)), followed by the posterior cerebral artery (56 (28,3%)). Serum levels of ANP had a median of 10,5 pg/mL (IQR 19) and NT-proBNP had a median of 113 ng/L (IQR 568). Two (1%) of the patients died during hospital stay.

There is some missing data in the analysis, namely information regarding the drug history of 3 patients (1,5%), the weight of twelve patients (6,1%) and height of fourteen patients (7,1%).

	N = 198
Demographic Characterization	
Age (years) (median, IQR)	65 [20,3]
Male sex (N, %)	122 [61,6]
Weight (kg) (median, IQR)	75,1 [14,7]
Height (cm) (median, IQR)	165 [13]
Cardiovascular Risk Factors N [%]	
Arterial Hypertension	123 [62,1]
Diabetes Mellitus	43 [21,7]
Smoking	38 [19,2]
Dyslipidemia	98 [49,5]
Atrial Fibrillation	14 [7,1]
Previous Stroke	42 [21,2]
Congestive Heart Failure	3 [1,5]
Ischemic Cardiopathy	29 [14,6]
Drugs N [%]	
ACEI	52 [26,7]
Beta-blocker	40 [20,5]
ARB	46 [23,6]
Diuretics	59 [30,3]
Event Characterization	
Stroke/TIA (No. Strokes) (N, %)	158 [79,8]
NIHSS admission (median, IQR)	4 [8,0]
NIHSS discharge (median, IQR)	2 [6,0]
r-TPA (N, %)	64 [32,3]
Rankin (median, IQR)	1,5 [3]
Etiology N [%]	
Large artery stenosis	37 [18,7]
Small-vessel occlusion	10 [5,1]
Cardioembolic	84 [42,4]
With AF	41 [20,7]
Undetermined	55 [27,8]
Other determined	12 [6,0]
Territory N [%]	
ACA	3 [1,5]
MCA	129 [65,2]
PCA	56 [28,3]
ICA	1 [0,5]
Simultaneous territories	9 [4,5]
Laboratory Tests	
ANP (pg/mL) (median, IQR)	10,5 [19]
NT-proBNP (ng/L) (median, IQR)	113 [568]
Complications	
Death (N, %)	2 [1,0]
Recurrence (N, %)	23 [11,6]

Table 1. Sample characterization (demographic data, cardiovascular risk factors, drugs, event characterization, etiology, affected territory, laboratory tests and complications).

2. Cardioembolic versus Noncardioembolic stroke

The next step was to compare the group of patients with cardioembolic and noncardioembolic strokes (Table 2).

No differences were observed in the demographic parameters between the two groups. Regarding the cardiovascular risk factors, patients with noncardioembolic events showed a higher frequency of arterial hypertension (69,3% vs. 52,4%, p=0,015), dyslipidemia (56,1% vs. 40,5%, p=0,029) and previous stroke (26,3% vs. 14,3%, p=0,041). The most prevalent cardioembolic stroke etiologies were AF (48,8%) and patent foramen ovale (34,5%). The severity of the event at admission, according to the NHISS, was significantly higher in the group of the cardioembolic strokes (6 vs. 4, p=0,012). There were no significant differences in the affected territories (p=0,139). The difference between NT-proBNP levels in cardioembolic stroke (344,5 ng/L, with IQR 1171) and noncardioembolic stroke (83 ng/L, with IQR 205) (Fig. 2) was statistically significant (p=0,001). Likewise, the difference between the median of values of ANP in cardioembolic (13 pg/mL, IQR 25) and noncardioembolic (8 pg/mL, IQR 13) stroke was significant (p=0,007) (Fig. 2).

	Cardioembolic (n=84)	**Noncardioembolic (n=114)**	**P**
Demographic Characterization			
Age (years) (median, IQR)	65 [25,8]	65 [17,3]	0,781
Male sex (N, %)	49 [58,3]	73 [64,0]	0,415
Weight (kg) (mean, SD)	75,2 [16,9]	75,1 [12,9]	0,951
Height (cm) (median, IQR)	166 [14,0]	165 [12,0]	0,990
Cardiovascular Risk Factors N [%]			
Arterial Hypertension	44 [52,4]	79 [69,3]	0,015*
Diabetes Mellitus	16 [19,0]	27 [23,7]	0,434
Smoking	15 [17,9]	23 [20,2]	0,682
Dyslipidemia	34 [40,5]	64 [56,1]	0,029*
Atrial Fibrillation	14 [16,6]	0 [0]	<0,001*
Previous Stroke	12 [14,3]	30 [26,3]	0,041*
Congestive Heart Failure	2 [2,4]	1 [0,9]	0,575

Ischemic Cardiopathy	16 [19,0]	13 [11,4]	0,133
Drugs N [%]			
ACEI	23 [27,4]	29 [26,1]	0,844
Beta-blocker	18 [21,4]	22 [19,8]	0,783
ARB	17 [20,2]	29 [26,1]	0,338
Diuretics	27 [32,1]	32 [28,8]	0,618
Event Characterization			
Stroke/TIA (No. Strokes) (N, %)	67 [79,8]	91 [79,8]	0,991
NIHSS admission (median, IQR)	6 [12,0]	4 [6,0]	0,012*
NIHSS discharge (median, IQR)	2 [7,0]	1 [4,0]	0,263
r-TPA (N, %)	28 [33,3]	36 [31,6]	0,794
Rankin (median, IQR)	2 [4,0]	1 [3,0]	0,177
Territory N [%]			
ACA	1 [1,2]	2 [1,8]	0,139
MCA	63 [75,0]	66 [57,9]	
PCA	18 [21,4]	38 [33,3]	
ICA	0 [0]	1 [0,9]	
Simultaneous territories	2 [2,4]	7 [6,1]	
Laboratory Tests			
ANP (pg/mL) (median, IQR)	13 [25]	8 [13]	0,007*
NT-proBNP (ng/L) (median, IQR)	344,5 [1171]	83 [205]	0,001*
Complications			
Death (N, %)	1 [1,2]	1 [0,9]	0,828
Recurrence (N, %)	12 [14,3]	11 [9,6]	0,314

Table 2. Sample characterization (demographic data, cardiovascular risk factors, drugs, event characterization, affected territory, laboratory tests and complications) in patients with cardioembolic and noncardioembolic events.

* Statistically significant p-values.

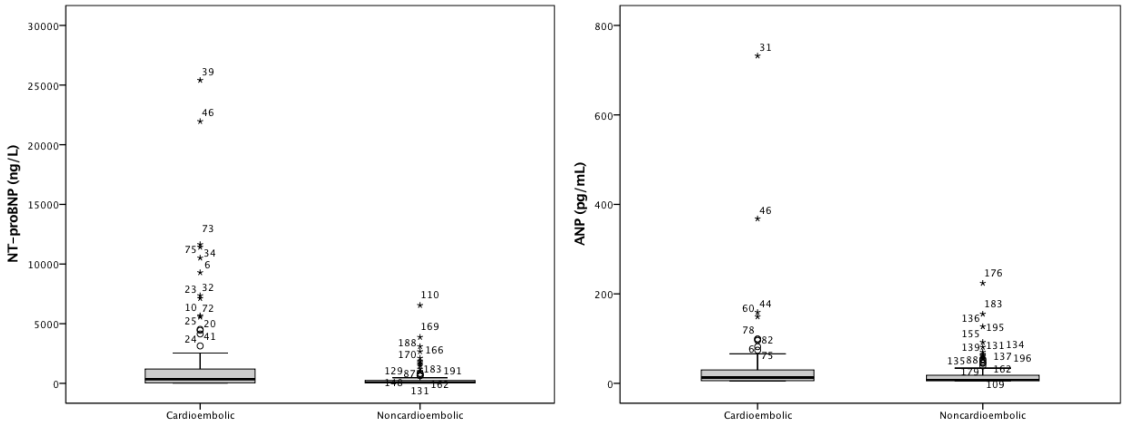

Figure 2. Serum levels of NT-proBNP and ANP in patients with cardioembolic and noncardioembolic events.

Receiver Operating Characteristic curves (ROC curves) were constructed in order to evaluate the ability of ANP and NT-proBNP to diagnose cardioembolic versus noncardioembolic stroke. The AUC for NT-proBNP was of 0,642 (95% CI 0,562 – 0,722, p=0,001) (Fig. 3). The selected cut-off value with highest sensitivity and specificity simultaneously was 125 ng/L, with a sensitivity of 60,7% and a specificity of 61,4%. The ROC curve for ANP had an AUC of 0,610 (95% CI 0,532 - 0,689, p=0,008) (Fig. 3). The cut-off value selected for this biomarker was 10,5 pg/mL, which had a sensitivity of 60,7% and a specificity of 57,9%. The comparison of both ROC curves showed a difference of AUC of 0,031 (95% CI -0,066 – 0,129), which was not significant (p=0,529).

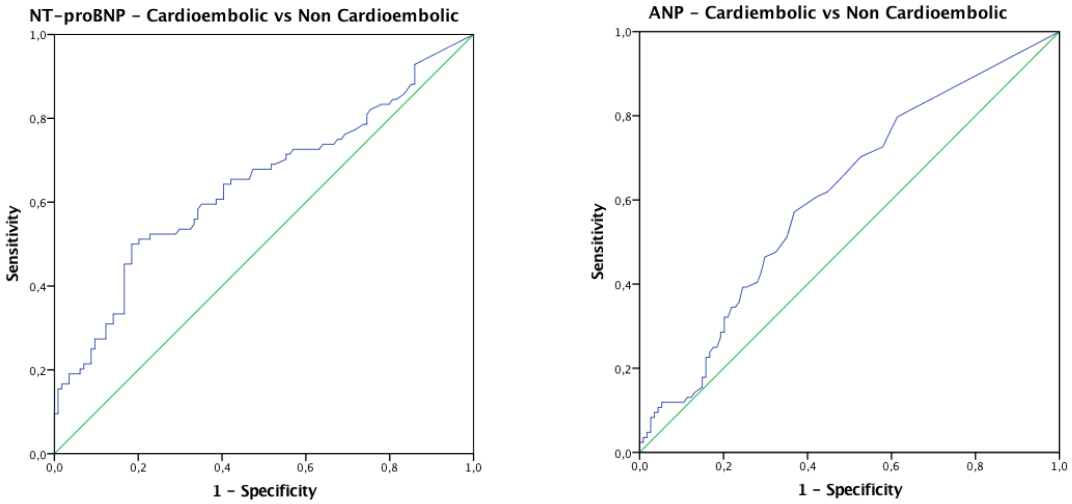

Figure 3. ROC curves representing the sensitivity and specificity of the biomarkers NT-proBNP and ANP in the diagnosis of cardioembolic versus noncardioembolic strokes, represented by the blue lines.

3. Cardioembolic with AF versus Noncardioembolic stroke

Forty-one patients with cardioembolic stroke had AF (48,8% of the patients with cardioembolic stroke). An analysis was made to compare this group with the group of noncardioembolic stroke (Table 3).

In the demographic characterization, patients with cardioembolic stroke and AF were significantly older (74 vs. 65 years, p<0,001), but there were no other significant differences. Individuals in the group of noncardioembolic events had a higher frequency of dyslipidemia (56,1% vs. 34,1%, p=0,016) and previous stroke (26,3% vs 9,8%, p=0,028), whereas in the cardioembolic with AF stroke group we observed a higher frequency of ischemic cardiopathy (26,8% vs. 11,4%, p=0,019). Individuals in the AF group most often were treated with diuretics (48,8% vs. 28,8%, p=0,021). The severity of the event was higher in patients with cardioembolic stroke and AF at admission and discharge (p<0,001 and p=0,003, respectively), as well as the morbidity at discharge (3 vs. 1, p<0,001). The differences between the affected territories were not significant. Serum NT-proBNP levels had a median value of 797 ng/L (IQR 4018) in cardioembolic events with AF and of 83 ng/L (IQR 205) in noncardioembolic events, the difference being statistically significant (p<0,001) (Fig. 4). ANP's median value was significantly higher in the cardioembolic strokes associated with AF group (19 pg/mL, IQR 41 vs 8 pg/mL, IQR 13, p<0,001) (Fig. 4).

	Cardioembolic with AF (n = 41)	**Noncardioembolic (n = 114)**	**P**
Demographic Characterization			
Age (years) (median, IQR)	74 [12]	65 [17,3]	<0,001*
Male sex (N, %)	24 [58,5]	73 [64,0]	0,533
Weight (kg) (mean, SD)	76,5 [17,9]	75,1 [12,9]	0,646
Height (cm) (median, IQR)	165 [14,0]	165 [12,0]	0,442
Cardiovascular Risk Factors N [%]			
Arterial Hypertension	29 [70,7]	79 [69,3]	0,864
Diabetes Mellitus	6 [14,6]	27 [23,7]	0,225
Smoking	4 [9,8]	23 [20,2]	0,131
Dyslipidemia	14 [34,1]	64 [56,1]	0,016*

Atrial Fibrillation	14 [34,1]	0 [0]	<0,001*
Previous Stroke	4 [9,8]	30 [26,3]	0,028*
Congestive Heart Failure	1 [2,4]	1 [0,9]	0,460
Ischemic Cardiopathy	11 [26,8]	13 [11,4]	0,019*
Drugs N [%]			
ACEI	14 [34,1]	29 [26,1]	0,330
Beta-blocker	13 [31,7]	22 [19,8]	0,122
ARB	14 [34,1]	29 [26,1]	0,330
Diuretics	20 [48,8]	32 [28,8]	0,021*
Event Characterization			
Stroke/TIA (No. Strokes) (N, %)	36 [87,8]	91 [79,8]	0,255
NIHSS admission (median, IQR)	11 [12,0]	4 [6,0]	<0,001*
NIHSS discharge (median, IQR)	4 [13,0]	1 [4,0]	0,003*
r-TPA (N, %)	21 [51,2]	36 [31,6]	0,025*
Rankin (median, IQR)	3 [2,0]	1 [3,0]	<0,001*
Territory N [%]			
ACA	0 [0]	2 [1,8]	0,218
MCA	32 [78,0]	66 [57,9]	
PCA	8 [19,5]	38 [33,3]	
ICA	0 [0]	1 [0,9]	
Simultaneous territories	1 [2,4]	7 [6,1]	
Laboratory Tests			
ANP (pg/mL) (median, IQR)	19 [41,0]	8 [13,0]	<0,001*
NT-proBNP (ng/L) (median, IQR)	797 [4018]	83 [205]	<0,001*
Complications			
Death (N, %)	1 [2,4]	1 [0,9]	0,460
Recurrence (N, %)	10 [24,4]	11 [9,6]	0,018*

Table 3. Sample characterization (demographic data, cardiovascular risk factors, drugs, event characterization, affected territory, laboratory tests and complications) in patients with cardioembolic events with AF and noncardioembolic events.

* Statistically significant p-values.

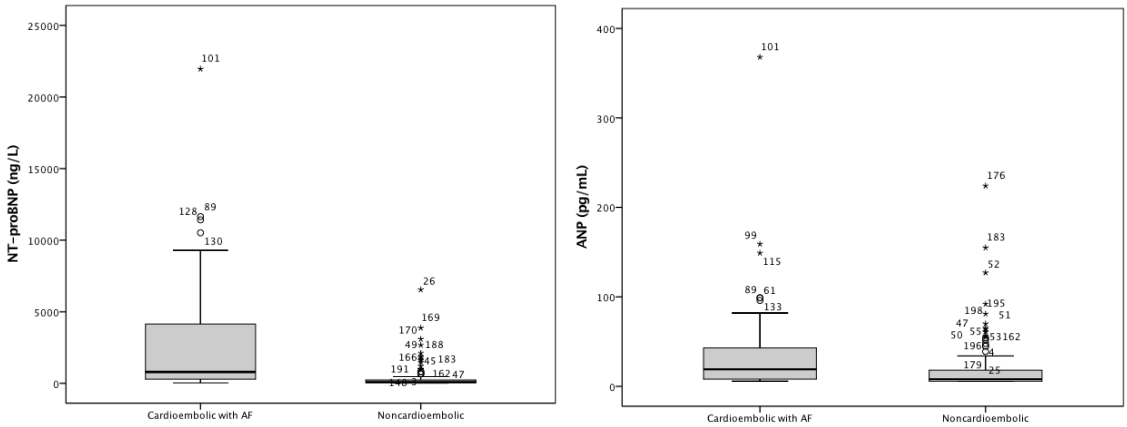

Figure 4. Serum levels of NT-proBNP and ANP in patients with cardioembolic events with AF and noncardioembolic events.

The ROC curve constructed to evaluate NT-proBNP's ability to diagnose cardioembolic events with AF versus noncardioembolic events had an AUC of 0,816 (95% CI 0,742 – 0,891, p<0,001) (Fig. 5), which was higher than the one for the diagnosis of cardioembolic versus noncardioembolic strokes (0,816 versus 0,642). The selected cut-off value was 247,5 ng/L, with 78,0% of sensitivity and 77,2% of specificity. The curve for ANP showed an AUC of 0,688 (95% CI 0,597-0,780, p<0,001), and the chosen cut-off point was 11,5 pg/mL, with 63,4% of sensitivity and 63,2% of specificity (Fig. 5). The difference of 0,128 (95% CI 0,023 – 0,232) between the ROC curves of both biomarkers was significant (p=0,016).

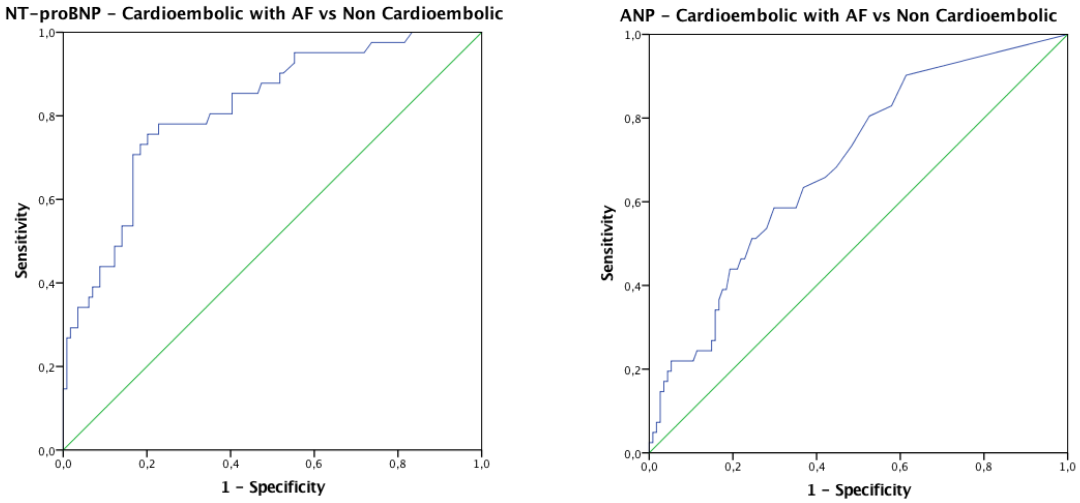

Figure 5. ROC curves representing the sensitivity and specificity of the biomarkers NT-proBNP and ANP in the diagnosis of cardioembolic events with AF versus noncardioembolic strokes, represented by the blue lines.

4. Cardioembolic versus Undetermined stroke

A comparison between the group of patients with cardioembolic stroke and stroke of undetermined etiology was performed next (Table 4).

There were no statistically significant differences in the demographic characterization or in risk factors between the two groups. Severity of neurology deficits at admission was higher in the cardioembolic group (6 vs. 4, p=0,008). Concerning the affected territory, in the undetermined etiology group, the MCA territory was the most frequently reported (50,9%), followed by PCA (38,2%), and territories other than the MCA were more frequently involved (p=0,045). Median NT-proBNP levels were 72 ng/L (IQR 217) in the undetermined etiology group, which was significantly inferior to the one obtained in the cardioembolic group (p=0,001) (Fig. 6). ANP levels (8pg/mL, IQR 11) showed a similar pattern (p=0,042) (Fig. 6).

	Cardioembolic (n=84)	**Undetermined etiology (n=55)**	**P**
Demographic Characterization			
Age (years) (median, IQR)	65 [25,8]	65 [21,0]	0,574
Male sex (N, %)	49 [58,3]	35 [63,6]	0,532
Weight (kg) (mean, SD)	75,2 [16,9]	74,8 [12,1]	0,874
Height (cm) (median, IQR)	166 [14,0]	165 [9,0]	0,913
Cardiovascular Risk Factors N [%]			
Arterial Hypertension	44 [52,4]	34 [61,8]	0,273
Diabetes Mellitus	16 [19,0]	11 [20,0]	0,890
Smoking	15 [17,9]	11 [20,0]	0,751
Dyslipidemia	34 [40,5]	30 [54,5]	0,104
Atrial Fibrillation	14 [16,6]	0 [0]	0,001*
Previous Stroke	12 [14,3]	12 [21,8]	0,251
Congestive Heart Failure	2 [2,4]	0 [0]	0,249
Ischemic Cardiopathy	16 [19,0]	4 [7,3]	0,053
Drugs N [%]			
ACEI	23 [27,4]	13 [24,1]	0,666
Beta-blocker	18 [21,4]	12 [22,2]	0,912

ARB	17 [20,2]	13 [24,1]	0,594
Diuretics	27 [32,1]	13 [24,1]	0,308
Event Characterization			
Stroke/TIA (No. Strokes) (N, %)	67 [79,8]	43 [78,2]	0,823
NIHSS admission (median, IQR)	6 [12,0]	4 [7,0]	0,008*
NIHSS discharge (median, IQR)	2 [7,0]	1,5 [3,0]	0,129
r-TPA (N, %)	28 [33,3]	18 [32,7]	0,941
Rankin (median, IQR)	2 [4,0]	1 [2,0]	0,153
Territory N [%]			
ACA	1 [1,2]	1 [1,8]	0,045*
MCA	63 [75,0]	28 [50,9]	
PCA	18 [21,4]	21 [38,2]	
ICA	0 [0]	1 [1,8]	
Simultaneous territories	2 [2,4]	4 [7,3]	
Laboratory Tests			
ANP (pg/mL) (median, IQR)	13 [25]	8 [11]	0,042*
NT-proBNP (ng/L) (median, IQR)	344,5 [1171]	72 [217]	0,001*
Complications			
Death (N, %)	1 [1,2]	1 [1,8]	1,000
Recurrence (N, %)	12 [14,3]	2 [3,6]	0,041*

Table 4. Sample characterization (demographic data, cardiovascular risk factors, drugs, event characterization, affected territory, laboratory tests and complications) in patients with cardioembolic and undetermined etiology strokes.

* Statistically significant p-values.

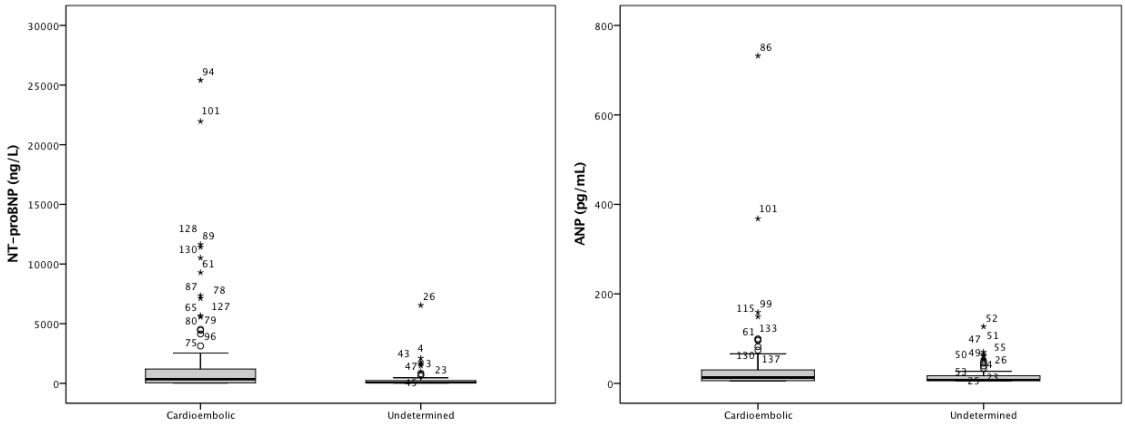

Figure 6. Serum levels of NT-proBNP and ANP in patients with cardioembolic and undetermined etiology events.

For the diagnosis of cardioembolic versus undetermined etiology stroke, NT-proBNP had an AUC of 0,672 (95% CI 0,582-0,762, p=0,001) (Fig. 7), and allowed the selection of the cut-off point 102,5 ng/L with sensitivity of 65,5% and specificity of 63,6%. The ROC curve for ANP, with an AUC of 0,601 (95% CI 0,504 – 0,698, p=0,044) (Fig. 7), provided a cut-off point of 11,5 pg/mL (sensitivity 57,1% and specificity 61,8%). The difference between the AUC of the two biomarkers was 0,070 (95% CI -0,044 – 0,186), not significant (p=0,227).

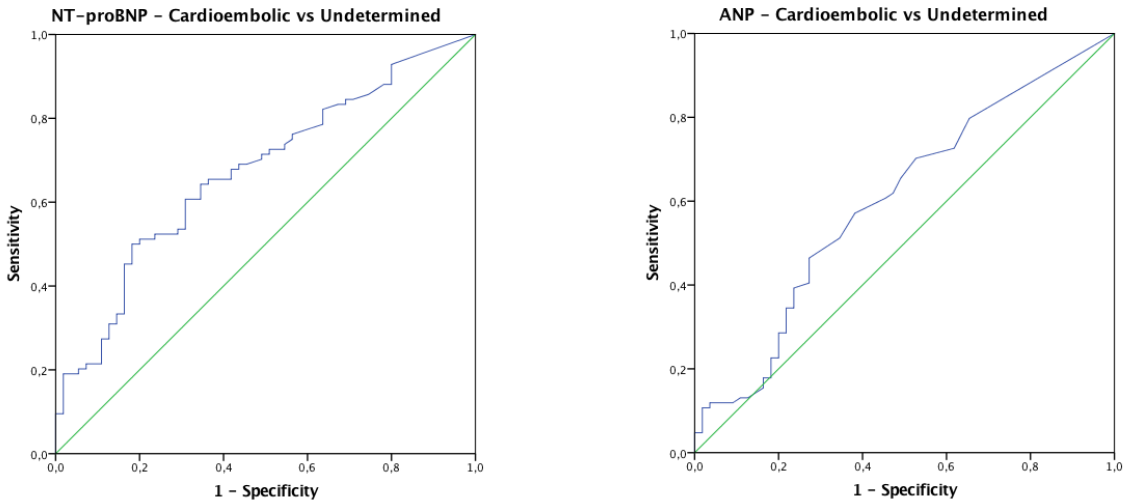

Figure 7. ROC curves representing the sensitivity and specificity of the biomarkers NT-proBNP and ANP in the diagnosis of cardioembolic versus strokes with undetermined etiology, represented by the blue lines.

5. Cardioembolic with AF versus Undetermined stroke

As shown in Table 5, patients with cardioembolic stroke associated to AF were older than patients with stroke of undetermined etiology (74 vs. 65 years, p=0,001). The first group also had a higher frequency of ischemic cardiopathy (26,8% vs. 7,3%, p=0,009). In contrast, patients with strokes of undetermined etiology had a more frequent history of dyslipidemia (54,5% vs. 34,1%, p=0,047). In terms of drugs, patients with cardioembolic strokes with AF showed higher consumption of diuretics comparing to the other group (48,8% vs. 24,1%, p=0,012). The severity and morbidity of the event were in agreement to what is reported above. Both biomarkers demonstrated a higher serum level in the group of cardioembolic stroke with AF comparing to the ones with undetermined etiology (p<0,001 on NT-proBNP and p=0,002 on ANP) (Fig. 8).

	Cardioembolic with AF (n = 41)	**Undetermined etiology (n = 55)**	**P**
Demographic Characterization			
Age (years) (median, IQR)	74 [12,0]	65 [21,0]	0,001*
Male sex (N, %)	24 [58,5]	35 [63,6]	0,612
Weight (kg) (mean, SD)	76,5 [17,9]	74,8 [12,1]	0,609
Height (cm) (median, IQR)	165 [14,0]	165 [9,0]	0,428
Cardiovascular Risk Factors N [%]			
Arterial Hypertension	29 [70,7]	34 [61,8]	0,363
Diabetes Mellitus	6 [14,6]	11 [20,0]	0,496
Smoking	4 [9,8]	11 [20,0]	0,172
Dyslipidemia	14 [34,1]	30 [54,5]	0,047*
Atrial Fibrillation	14 [34,1]	0 [0]	<0,001*
Previous Stroke	4 [9,8]	12 [21,8]	0,117
Congestive Heart Failure	1 [2,4]	0 [0]	0,427
Ischemic Cardiopathy	11 [26,8]	4 [7,3]	0,009*
Drugs N [%]			
ACEI	14 [34,1]	13 [24,1]	0,281
Beta-blocker	13 [31,7]	12 [22,2]	0,298
ARB	14 [34,1]	13 [24,1]	0,281

Diuretics	20 [48,8]	13 [24,1]	0,012*
Event Characterization			
Stroke/TIA (No. Strokes) (N, %)	36 [87,8]	43 [78,2]	0,222
NIHSS admission (median, IQR)	11 [12,0]	4 [7,0]	<0,001*
NIHSS discharge (median, IQR)	4 [13,0]	1,5 [3,0]	0,002*
r-TPA (N, %)	21 [51,2]	18 [32,7]	0,068
Rankin (median, IQR)	3 [2,0]	1 [2,0]	<0,001*
Territory N [%]			
ACA	0 [0]	1 [1,8]	0,091
MCA	32 [78,0]	28 [50,9]	
PCA	8 [19,5]	21 [38,2]	
ICA	0 [0]	1 [1,8]	
Simultaneous territories	1 [2,4]	4 [7,3]	
Laboratory Tests			
ANP (pg/mL) (median, IQR)	19 [41,0]	8 [11,0]	0,002*
NT-proBNP (ng/L) (median, IQR)	797 [4018]	72 [217,0]	<0,001*
Complications			
Death (N, %)	1 [2,4]	1 [1,8]	1,000
Recurrence (N, %)	10 [24,4]	2 [3,6]	0,002*

Table 5. Sample characterization (demographic data, cardiovascular risk factors, drugs, event characterization, affected territory, laboratory tests and complications) in patients with cardioembolic events with AF and undetermined etiology events.

* Statistically significant p-values.

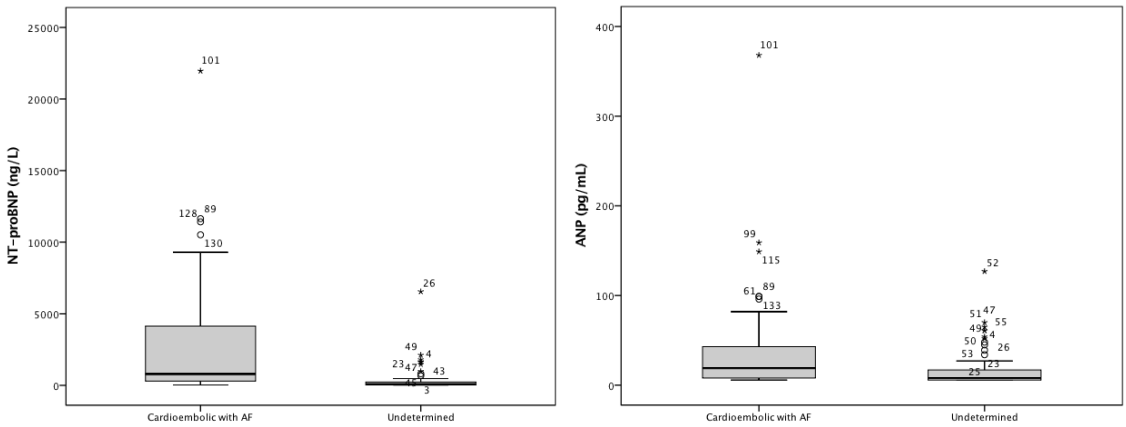

Figure 8. Serum levels of NT-proBNP and ANP in patients with cardioembolic events with AF and undetermined etiology events.

The precision of the biomarkers for the diagnosis of cardioembolic events with AF versus undetermined etiology was studied next. NT-proBNP, had an AUC of 0,830 (95% CI 0,750 - 0,911, p<0,001) (Fig. 9), and the selected cut-off value of 247 ng/L had a sensitivity of 78% and specificity of 76,4%. ANP determined a ROC curve with an AUC of 0,680 (95% CI 0,573 - 0,787, p=0,003) (Fig. 9), in which the point with the highest sensitivity (63,4%) and specificity (61,8%) simultaneously, matched the cut-off value of 11,50 pg/mL. There was a difference of 0,150 (95% CI 0,034 – 0,266) between the curves of both biomarkers, which was significant (p=0,011).

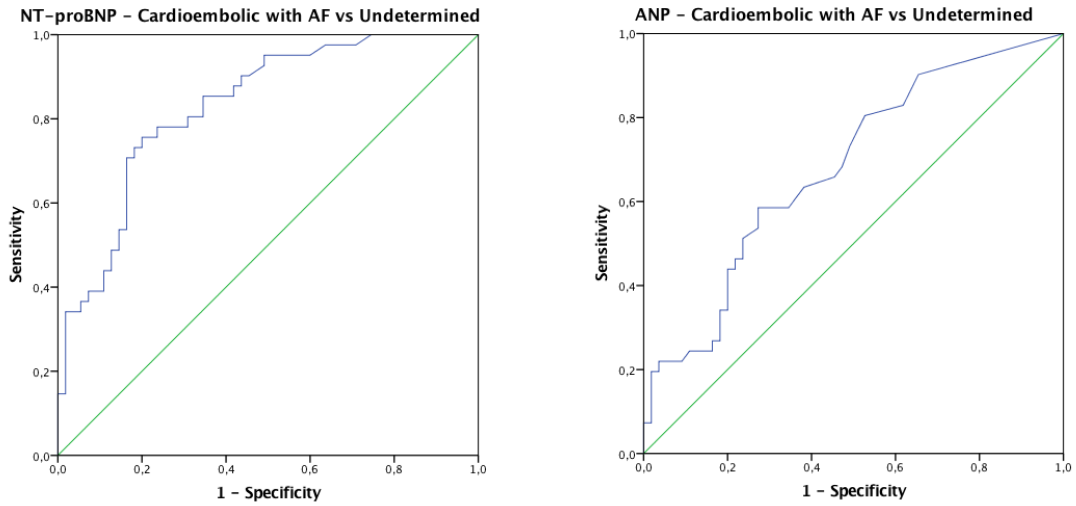

Figure 9. ROC curves representing the sensitivity and specificity of the biomarkers NT-proBNP and ANP in the diagnosis of cardioembolic events with AF versus undetermined strokes, represented by the blue lines.

6. Cardioembolic stroke versus Other stroke etiologies

At last, an analysis to determine the significance of the differences between the group of patients with cardioembolic strokes and the patients with strokes of other etiologies, such as large artery stenosis, small-vessel occlusion and other determined etiologies (including carotid and vertebral artery dissection), was carried out (Table 6).

The serum level of NT-proBNP showed a median of 95 ng/L (IQR 193,0) in the other stroke etiologies group, significantly lower than the serum level in the cardioembolic stroke group (p=0,021) (Fig. 10). Median ANP's serum levels were 8 pg/mL (IQR 13,0), also lower than found in the cardioembolic group (p=0,014) (Fig. 10).

	Cardioembolic (n=84)	**Other stroke etiologies, except U (n=59)**	**P**
Demographic Characterization			
Age (years) (median, IQR)	65 [25,8]	65 [16,0]	0,936
Male sex (N, %)	49 [58,3]	38 [64,4]	0,464
Weight (kg) (mean, SD)	75,2 [16,9]	75,3 [13,7]	0,968
Height (cm) (median, IQR)	166 [14,0]	165 [13,0]	0,900
Cardiovascular Risk Factors N [%]			
Arterial Hypertension	44 [52,4]	45 [76,3]	0,004*
Diabetes Mellitus	16 [19,0]	16 [27,1]	0,254
Smoking	15 [17,9]	12 [20,3]	0,709
Dyslipidemia	34 [40,5]	34 [57,6]	0,043*
Atrial Fibrillation	14 [16,6]	0 [0]	<0,001*
Previous Stroke	12 [14,3]	18 [30,5]	0,019*
Congestive Heart Failure	2 [2,4]	1 [1,7]	1,000
Ischemic Cardiopathy	16 [19,0]	9 [15,3]	0,557
Drugs N [%]			
ACEI	23 [27,4]	16 [28,1]	0,928
Beta-blocker	18 [21,4]	16 [28,1]	0,570
ARB	17 [20,2]	10 [17,5]	0,281
Diuretics	27 [32,1]	19 [33,3]	0,882
Event Characterization			

Stroke/TIA (No. Strokes) (N, %)	67 [79,8]	48 [81,4]	0,813
NIHSS admission (median, IQR)	6 [12,0]	4 [6,0]	0,111
NIHSS discharge (median, IQR)	2 [7,0]	1 [6,0]	0,692
r-TPA (N, %)	28 [33,3]	18 [30,5]	0,722
Rankin (median, IQR)	2 [4,0]	1 [3,0]	0,400
Territory N [%]			
ACA	1 [1,2]	1 [1,7]	0,550
MCA	63 [75,0]	38 [64,4]	
PCA	18 [21,4]	17 [28,8]	
ICA	0 [0]	0 [0]	
Simultaneous territories	2 [2,4]	3 [5,1]	
Laboratory Tests			
ANP (pg/mL) (median, IQR)	13 [25,0]	8 [13,0]	0,014*
NT-proBNP (ng/L) (median, IQR)	344,5 [1171,0]	95 [193,0]	0,021*
Complications			
Death (N, %)	1 [1,2]	0 [0]	1,000
Recurrence (N, %)	12 [14,3]	9 [15,3]	0,872

Table 6. Sample characterization (demographic data, cardiovascular risk factors, drugs, event characterization, affected territory, laboratory tests and complications) in patients with cardioembolic events and other etiologies except undetermined (U).

* Statistically significant p-values.

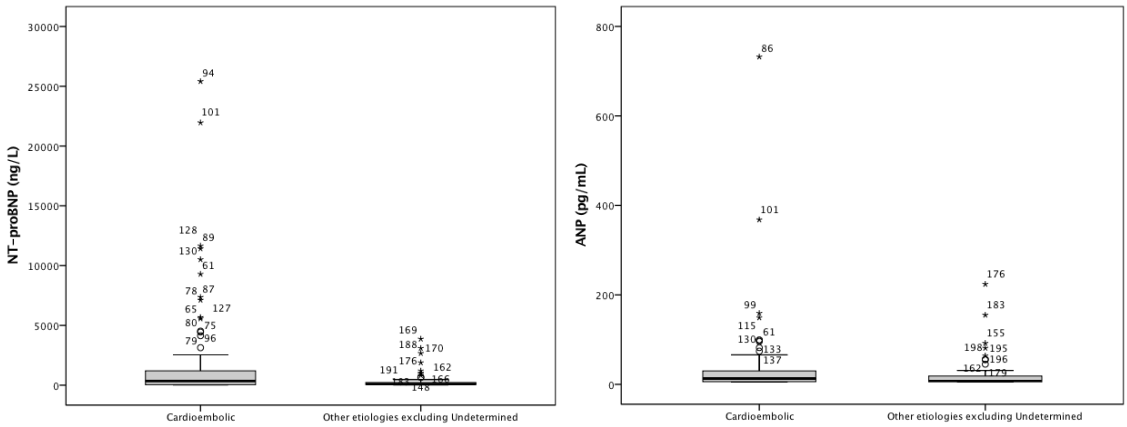

Figure 10. Serum levels of NT-proBNP and ANP in patients with cardioembolic events and other etiologies except cardioembolic (C) and undetermined (U).

We also analyzed the ability of the biomarkers to diagnose cardioembolic stroke versus stroke of other etiologies, such as large artery stenosis, small-vessel occlusion and other determined etiologies (including carotid and vertebral artery dissection). The ROC curve constructed for NT-proBNP had an AUC of 0,614 (95% CI 0,522-0,706, p=0,021) (Fig. 11). The chosen cut-off point was 109,5 ng/L, with a sensitivity of 64,3% and a specificity of 54,2%. With ANP, the ROC curve had an AUC of 0,619 (95% CI 0,525-0,714, p=0,015) (Fig. 11). A sensitivity of 60,7% and a specificity of 61% could be achieved with the cut-off value of 10,5 pg/mL. The comparison between the two curves represented below showed a nonsignificant difference (p=0,924) of 0,006 (95% CI -0,109 – 0,120).

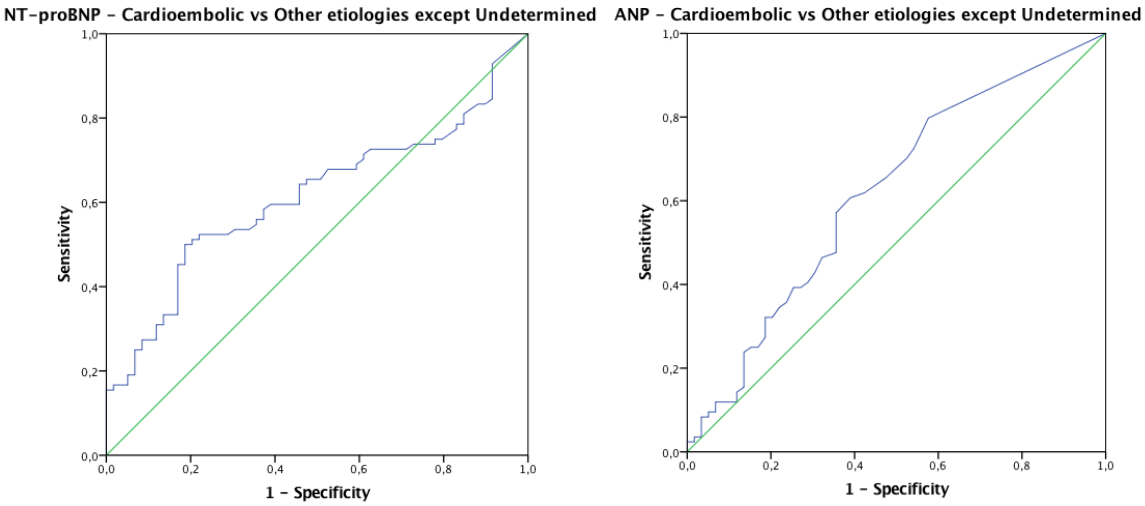

Figure 11. ROC curves representing the sensitivity and specificity of the biomarkers NT-proBNP and ANP in the diagnosis of cardioembolic events versus other etiologies except and undetermined, represented by the blue lines.

Discussion

In patients with stroke of cardioembolic origin due to AF, the start of therapy with oral anticoagulants such as vitamin K antagonists or NOACs, is recommended for secondary stroke prevention (Kernan et al., 2014). Therefore, it is of great importance to diagnose AF in patients with ischemic events in order to establish these measures and avoid recurrent events.

In this study, an analysis and comparison of the accuracy of the biomarkers NT-proBNP and ANP to identify AF in patients with ischemic stroke was performed. It was hypothesized that ANP would have higher diagnostic acuity than NT-proBNP, since it is mainly secreted by the atria, and AF originates in these cardiac chambers (Yasue et al., 1994). It is important to mention that NT-proBNP has a half-life of 120 minutes (Weber, Mitrovic & Hamm, 2006) while ANP has a much shorter half-life, of 2-3 minutes (Yandle et al., 1986).

There are few studies that compared the accuracy of the biomarkers BNP/NT-proBNP and ANP to diagnose AF in patients with ischemic stroke. The present study aims to fill that gap.

Several studies have shown the utility of NT-proBNP for the identification of AF and of the risk of developing AF (Li et al., 2018; Mei, Jiefu & Yingying, 2009; Svennberg et al., 2016). Some studies considered its role in the risk prediction of thromboembolic events and cardiovascular mortality in patients with this arrhythmia (Hijazi et al., 2012, 2013). BNP, in patients with AF, relates to the probability of progression to more persistent and permanent forms of AF and to the risk of major adverse cardiovascular or neurological events (Inohara et al., 2019). These findings led to the inclusion of NT-proBNP in a risk score that predicts the incidence of stroke and systemic embolism in patients with AF. The ABC (age, biomarkers, clinical history) score is based in four variables: two biomarkers, NT-proBNP and high-sensitivity cardiac troponin, age and previous stroke/TIA history. This score showed a higher accuracy than CHA_2DS_2-VASc for the prediction of stroke in patients with AF (Hijazi et al., 2016).

Higher levels of NT-proBNP were associated to the diagnosis of AF and to an increased risk of cardioembolic stroke, but not to other subtypes of ischemic stroke (Berntsson et al., 2014). Additionally, many have concluded that NT-proBNP and BNP

are useful for the differential diagnosis of cardioembolic stroke from other subtypes of ischemic stroke, namely when associated with AF (Fonseca et al., 2011; Hajsadeghi et al., 2013; Naya et al., 2008). The meta-analysis by Llombart et al. (2015) showed that the serum levels of NT-proBNP and BNP were significantly elevated in cardioembolic stroke, with a sensitivity/specificity to distinguish them from other etiologies of 40%/90.1% in the highest quartile and 86.3%/36.2% in the lowest quartile for NT-proBNP, and of 42.3%/90.7% in the highest quartile and 93.68%/41.94% for the lowest quartile for BNP. The meta-analysis by Bai et al. (2018) compared the ability of BNP and NT-proBNP to diagnose cardioembolic stroke versus other etiologies of ischemic stroke, and concluded that BNP had a higher sensitivity (0.65 (95% CI 0.63-0.68) vs 0.55 (95% CI 0.52–0.59)) while NT-proBNP had a higher specificity (0.93 (95% CI 0.91–0.94) vs 0.85 (95% CI 0.83-0.87)).

Some investigators studied the role of NT-proBNP and similar biomarkers for the identification of AF during the follow-up of patients with ischemic and cryptogenic stroke, showing positive results (Fonseca, et al., 2014; Rodriguéz-Yañez, et al., 2013; Shibazaki et al., 2012; Wacther et al., 2012; Wasser et al., 2020), as well as in the reclassification of undetermined stroke etiology as cardioembolic (Rodríguez-Yáñez et al., 2009).

The role of ANP has also been investigated. Estrada et al. (1994) showed that this biomarker was significantly elevated in patients with ischemic stroke in comparison to controls, but it did not correlate to the etiology of stroke. Elevated levels of this biomarker were shown to predict the incidence of AF in a male population (Mandalenakis et al., 2014). It was also useful for the identification of AF and of cardioembolic stroke associated AF in both acute and chronic stages of ischemic stroke (Sato et al., 1995). A study by Shiroto et al. (2017), which evaluated the predictive value of ANP for the identification of pAF in patients with ischemic stroke, showed a sensitivity of 92% and a specificity of 51% with a cut-off value of 42,6 mg/dL. It also showed that levels of the biomarker were increased in patients with AF compared to patients in sinus rhythm (42 [26-72] mg/dL), with superior values in chronic AF (228 [120-392] mg/dL), than in pAF (97 [50-157] mg/dL).

In recent years, many studies used MR-proANP (mid-regional pro-atrial natriuretic peptide), which is a part of the pro-hormone of ANP with a longer half-life

(Morgenthaler et al., 2004; Rosenzweig & Seidman, 1991). This biomarker has been shown to be a good indicator of prognosis in the acute phase of an ischemic stroke, predicting the functional outcomes and the mortality at 90-days after the event (De Marchis et al., 2018; Katan et al., 2010). It is also a useful marker of cardioembolic etiology and of AF in patients with an acute ischemic stroke (De Marchis et al., 2018; Katan et al., 2010). The pro-ANP molecule is also a useful marker of cardioembolic stroke according to the work by Rodríguez-Yáñez et al. (2009). Studies showed that levels of MR-proANP were associated with an increase in the risk of ischemic stroke, particularly cardioembolic (Berntsson et al., 2014, 2017; Katan et al., 2016), of AF and of strokes associated with AF, prospectively (Berntsson et al., 2014, 2017). Other authors also showed that MR-proANP was a good predictor of the duration of the episode of AF, with higher levels in AF with a duration > 48h than with ≤ 48 hours, for which it displayed a higher precision than NT-proBNP (Legallois et al., 2017; Meune et al., 2011).

In this study, both NT-proBNP and ANP proved to be useful for the diagnosis of cardioembolic versus noncardioembolic stroke, and their diagnostic acuity was not significantly different. Likewise, after evaluating the ability to diagnose cardioembolic versus stroke of undetermined etiology, the results revealed that both biomarkers could be similarly suitable. Based on the results, it is possible to state that NT-proBNP and ANP are useful for the diagnosis of cardioembolic events, both versus noncardioembolic and undetermined etiology events. The results that were obtained for ANP were similar to the ones reported in previous studies that evaluated ANP pro-hormones: Rodríguez-Yáñez et al. (2009), Katan et al. (2010) and De Marchis et al. (2018).

Many conditions can cause a cardioembolic stroke, the most prevalent being AF (Kamel & Healey, 2017). Other pathologies associate to cardioembolic stroke are heart failure, recent myocardial infarction, patent foramen ovale, prosthetic heart valves and infectious endocarditis (Kamel & Healey, 2017). In the present study, 48,8% of the cardioembolic strokes were associated to AF. Both NT-proBNP and ANP were useful for the diagnosis of cardioembolic stroke with AF versus noncardioembolic and undetermined etiology stroke, but NT-proBNP showed a superior acuity.

In summary, the results showed that both biomarkers are suitable for the diagnosis of cardioembolic stroke, and that the diagnostic precision increases for the diagnosis of cardioembolic stroke associated to AF. For the later circumstance, NT-proBNP proved to have a higher acuity than ANP.

Lastly, the results also showed that both biomarkers can be useful for the identification of cardioembolic stroke versus stroke resulting from large artery atherosclerosis, small-vessel occlusion, and other determined etiologies, none of them being superior to the other.

These results do not corroborate our initial hypothesis, that ANP would have a higher accuracy for the diagnosis of AF than NT-proBNP. Likewise, ANP did not show a higher acuity than BNP for the diagnosis of AF in the article by Shiroto et al. (2017), in which the difference between the areas of ROC curves of these two biomarkers (ANP: AUC of 0,76 and BNP: AUC of 0,80) for the diagnosis of pAF in patients with ischemic stroke was not significant. In the work by Wachter et al. (2012), ROC curves for the same objective were determined for BNP (AUC 0,747 (95% CI: 0,663–0,831)), NT-proBNP (AUC 0.638 (95% CI: 0.531–0.744)) and NT-proANP (AUC 0.663 (95% CI: 0.566–0.761)).

Several theories can explain the discrepancy between the study's hypothesis and the present results. First, as mentioned above, ANP's plasma half-life is shorter than NT-proBNP's (Weber et al., 2006; Yandle et al., 1986). The serum levels of both biomarkers were determined using the same blood sample for each patient, collected up to 72 hours after the beginning of the symptoms. Thus, the levels of ANP in patients with AF could be less elevated than the levels of NT-proBNP, due to its faster clearance.

Stroke of thromboembolic etiology is associated with other modifications in the atria, such as fibrosis, chamber dilation, changes in contractility with an increase in the filling pressures, anatomical characteristics of the left atrial appendage, genetic mutations, coagulation disturbances (in patients with a unfavorable atrial anatomy) and several dysrhythmias (Elkind, 2018; Kamel et al., 2015). This concept of atrial cardiopathy might be both a cause or a consequence of AF (Kamel et al., 2015). The work by Cao et al. (2010) revealed that the expression of pro-BNP mRNA in right atrial appendage tissue was significantly more augmented in patients with paroxysmal and

persistent AF in comparison to sinus rhythm, while pro-ANP mRNA was only higher in paroxysmal AF. This study also showed that atrial tissue has more fibrosis in persistent AF than in pAF. They associated the lower expression of pro-ANP mRNA in persistent AF with the more prominent fibrosis found in the tissue of these patients. Furthermore, the diference between the gene expression of ANP and BNP in permanent AF was justified by the atria having a high capability to increase BNP production but not ANP production as concluded in the article by Wei et al. (1993). Therefore, we are presented with the possibility that atrial cardiopathy, here in the form of fibrosis, can impair the release of atrial natriuretic peptides from the atrial tissue over time, and weaken the utility of these biomarkers. Also, the results reported by Wei et al. (1993) may justify the more significant elevation of NT-proBNP than ANP found in this study.

Processing and release of the two biomarkers is distinct. While ANP is stored in granules and released into the circulation after myocyte stretch, BNP's synthesis and secretion occurs in bursts and its gene expression increases in response to myocyte stretch (Daniels & Maisel, 2007; De Lemos et al., 2003). This difference might explain the higher acuity of NT-proBNP for the diagnosis of AF, since the release of ANP into the circulation may become impared over time due to storage depletion. Accordingly, in dogs with pacing-induced heart failure, it was found that there is a mitigation of the increase of plasma ANP as acute heart failure progresses, especially after one week (Moe et al., 1991). This phenomenon could be due to a limitation in the stretching capacity of the atrial tissue and to the limited storage of the biomarker inside the myocytes (Moe et al., 1991). So, in patients with longer duration of AF (permanent or persistent), the serum quantity of ANP might not be significantly elevated, lowering its sensitivity for the diagnosis of this arrhythmia in comparison to NT-proBNP.

In contrary, the study by Shiroto et al. (2017) mentions that ANP serums levels are higher in patients with chronic AF than in pAF (p=0,001). Therefore, this biomarker could be less sensible for the detection of paroxysmal events due to their short duration in which the release of ANP will not be as distinct.

Some studies mention that an increase in right atrium stretch is the primary cause of ANP secretion, showing a stronger relation to the release of the biomarker than the same changes in the left atrium (Edwards et al., 1988; Globits et al., 1998).

Since AF is an arrhythmia originated predominantly in the left atrium, this might result in an impairment of the diagnostic ability of the mentioned biomarker.

Lastly, both biomarkers can be secreted by atrial and ventricular tissue in pathological conditions (Yasue et al., 1994). As mentioned by Saito et al. (1989) and Moe et al. (1991), in the pathological heart with congestive heart failure, ventricles are an important source of ANP and the increase of the genetic expression of ANP is more prominent in the ventricular than in the atrial tissue. It is also referred that the rise in this biomarker's secretion occurs at a higher speed after a stimulus in the ventricles (Saito et al., 1989). In the cohort used for this study, three patients had the diagnosis of congestive heart failure. However, we could infer that other pathologic heart conditions present in this study (for example, arrhythmias, coronary heart disease, congenital malformations or valve pathology) may also result in release of ANP from the ventricles. This data could justify the lower precision for the diagnosis of AF by ANP, since its release by cardiac chambers other than the left atrium in pathological heart conditions is so distinct.

This study has several limitations. The first limitation relates to the size of the sample, since the sample is smaller than the one previously mentioned as ideal. Therefore, a larger sample could allow the achievement of more precise results and a smaller sampling error. Second, the fact that a retrospective cohort was used is a limitation, since the probability of having missing data is higher is this type of study. In fact, it was not possible to gather information regarding the drug history of three patients and information about the weight and height of twelve and fourteen subjects, respectively. As third and last limitation, and as was mentioned above, the heart monitoring methods routinely used during the etiology investigation of an ischemic stroke have a relatively low sensitivity for the diagnosis of AF (Thomas & Lerman, 2011). In this study, the only methods used were the standard ECG and the 24-hour Holter, as recommended in the protocols for clinical trials. The use of short-term cardiac monitorings like these decreases the likelihood of detecting episodes of paroxysmal AF, since these are transient and usually last less than 48 hours (Kirchhof et al., 2016). Thus, prolonged heart monitoring methods would allow a higher detection rate of these transient events (Dahal et al., 2016; Rabinstein, 2014;

Tsivgoulis et al., 2019). Therefore, there is a substantial probability that AF was not identified in all of the patients with this arrhythmia as the cause of the ischemic event.

We recommend that studies using methods of prolonged heart monitoring are carried out, in order to increase the sensitivity of the diagnosis of transient arrhythmic events, and to study the biomarker's precision for the identification of paroxysmal AF. We also advise the use of the biomarker MR-proANP instead of ANP in future studies, given that this ANP pro-hormone has a lower binding rate to the receptors of natriuretic peptides and no interactions with other proteins. These characteristics give it a longer half-life and greater analytic stability, in comparison to ANP (Idzikowska & Zielińska, 2018; Morgenthaler et al., 2004).

Conclusion

In conclusion, we observed that both NT-proBNP and ANP could be useful for the diagnosis of cardioembolic stroke associated to AF. However, NT-proBNP showed higher accuracy. Therefore, NT-proBNP should remain as the biomarker of choice for the diagnosis of AF during the etiological investigation of patients with ischemic stroke.

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This work was partially presented at the Congresso de Neurologia 2019 as an E-poster. The abstract was posteriorly published on the scientific journal Sinapse (Volume 19, Supplement 1, 2019) (**Annex 1**).

It was later partially presented at the 14th Congresso Português do AVC as an oral communication (**Annex 2**).

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Annex

Annex 1

derá dever-se à manutenção de tratamento antiepilético, pelo que não foi possível determinar fatores de risco de recorrência.

EP-077 DISARTRIA E DISFONIA PAROXÍSTICAS ASSOCIADAS A DOLICOECTASIA DA ARTÉRIA VERTEBRAL

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Introdução: A ocorrência de disartria intermitente/paroxística por disfunção do tronco cerebral é habitualmente uma consequência de lesão de natureza vascular ou desmielinizante. São raras as descrições de disartria paroxística por compressão neurovascular.

Caso clínico: Homem de 84 anos, observado por episódios súbitos de disartria e disfonia. Esta manifestação tinha 3 meses de evolução, com episódios de duração inferior a 1 minuto e que se repetiam frequentemente (10-20 vezes/dia), não se identificando quaisquer precipitantes. No último mês, começara também com cefaleia persistente occipital esquerda. No EN apresentava parésia facial central esquerda e parésia da língua com atrofia e fasciculações da hemilíngua esquerda. Sem disfonia, disartria, alterações do palato ou disfagia. Sem ataxia ou sinais de vias longas. À observação por ORL (já sob terapêutica) a laringoscopia não mostrou alterações e o EEG era normal. A RM de crânio e pescoço revelou a existência de contacto neurovascular por dolicoectasia da artéria vertebral, afectando os IX, X e XI nervos cranianos (NC) esquerdos e possivelmente o XII NC ipsilateral; em complemento, a TC cervical excluiu lesões no trajeto ósseo destes nervos. Os episódios remitiram totalmente com eslicarbazepina 400mg, a par de melhoria da dor occipital.

Conclusão: Relata-se um caso de disartria e disfonia paroxísticas associadas a compressão neurovascular de nervos cranianos baixos por dolicoectasia da artéria vertebral, associado a síndrome do côndilo occipital. Pelas características do quadro e a resposta à eslicarbazepina deve admitir-se um mecanismo fisiopatológico similar ao da nevralgia dos V e IX NC. A atrofia da hemilíngua esquerda e a presença de dor occipital sugerem o envolvimento direto do XII NC na génese destes episódios. Adicionalmente, o caso sugere que a dolicoectasia da artéria vertebral possa ser incluída nas causas de síndrome do côndilo occipital.

EP-078 ACUIDADE DO PÉPTIDEO ATRIAL NATRIURÉTICO PARA DIAGNÓSTICO DE FIBRILHAÇÃO AURICULAR EM DOENTES COM AVC ISQUÉMICO

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Introdução: A fibrilhação auricular (FA) paroxística é responsável por 10-15% AVC criptogénicos. Vários estudos mostraram a utilidade do N-terminal do péptido natriurético cerebral (NT-proBNP) na identificação de AVC cardioembólico associado a FA. Por ser produzido nas aurículas, o péptido atrial natriurético (ANP) pode ter maior acuidade que o NT-proBNP para o diagnóstico de FA.

Objetivo: Determinar se o ANP tem maior acuidade que o NT-proBNP para o diagnóstico de FA, em doentes com AVC isquémico.

Metodologia: Realizámos um estudo observacional utilizando uma coorte retrospetiva de doentes internados de 08/2012 a 10/2013 na Unidade de AVC de um hospital universitário. Critérios de inclusão: doentes com AVC isquémico agudo e amostras de soro disponíveis em Biobanco. Critérios de exclusão: TFG<30mL/min; colheitas de sangue >72 horas após o início de sintomas. A etiologia do AVC foi determinada com a classificação TOAST. A análise estatística incluiu a determinação de curvas ROC.

Resultados: Foram incluídos 204 doentes com uma mediana de idade de 65 anos, 61.8% eram do sexo masculino. A curva ROC para o diagnóstico de eventos cardioembólicos com FA versus não cardioembólicos obteve uma AUC de 0.83 (IC 95% 0.76-0.90) com NT-proBNP e 0.66 (IC 95% 0.56-0.75) para o ANP. No diagnóstico de eventos cardioembólicos com FA versus indeterminados, com NT-proBNP a AUC foi 0.83 (IC 95% 0.75-0.90) e com ANP de 0.62 (IC 95% 0.52-0.73).

Discussão/Conclusões: O NT-proBNP, comparativamente ao ANP, teve maior acuidade diagnóstica para FA, o que pode dever-se ao facto dos AVC tromboembólicos se associarem a alterações nas aurículas que não apenas FA e à diminuição da libertação de ANP com episódios repetidos de FA e instalação de insuficiência cardíaca.

Conflitos de interesses: Financiado pela Bolsa CHULN/FMUL, GAPIC.

EP-079 AS ATIPIAS DE UMA SÍNDROME DE ENCEFALOPATIA POSTERIOR REVERSÍVEL: DO COMA SÚBITO AO PADRÃO IMAGIOLÓGICO INCOMUM

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Introdução: A Síndrome de Encefalopatia Posterior Reversível (PRES) é caracterizada pela presença de sintomas neurológicos agudos/subagudos diversos, associados a um padrão imagiológico distintivo e potencialmente reversível – tipicamente, edema vasogénico subcortical parietal e occipital bilateral. A quimioterapia, a hipertensão arterial e a sépsis/infecção severa são causas descritas de PRES.

Caso Clínico: Homem de 37 anos, sem antecedentes de relevo à excepção de diagnóstico recente de linfoma difuso de grandes células B primário do testículo, é admitido no Serviço de Urgência com neutropenia febril e deterioração do estado de consciência, sete dias após terminar o segundo ciclo de quimioterapia - que incluía rituximab, ciclofosfamida, vincristina, doxorrubicina, dexametasona, metotrexato e citarabina.

À admissão, encontrava-se hipertenso (175/92 mmHg), febril (39.5ºC) e sonolento, apresentando rápida deterioração neurológica até ao coma. Analiticamente, com pancitopenia severa. TC cranioencefálica com hipodensidades talâmicas bilaterais; ressonância magnética (RM) com áreas hiperintensas em T2/FLAIR envolvendo predominantemente tálamos, cápsula interna, mesencéfalo e ponte. Análise de LCR com hiperproteinorráquia, sem outras alterações.

Iniciada antibioterapia empírica, terapêutica de controlo tensional e de suporte e admissão subsequente na Unidade de Cuidados Intensivos (UCI). À data da transferência da UCI, 5 dias após admissão, o doente apresentava-se desorientado, disártrico e tetraparético; com melhoria clínica progressiva posterior. Quatro semanas após admissão, uma nova RM revelava regressão marcada das lesões talâmicas e nova lesão no corpo

Annex 2

METODOLOGIA | Os doentes adultos com diagnóstico genético (mutação no gene GLA) e fenótipo clássico de DF, ainda sem expressão clínica de DVC, foram recrutados no nosso hospital. Monitorizámos a velocidade do fluxo sanguíneo cerebral (VFSC) com Doppler transcraniano nas artérias cerebral média e cerebral posterior (ACP), a pressão arterial (PA), frequência cardíaca e dióxido de carbono expirado (CO_2) de forma não invasiva. A ARC foi avaliada pela função de transferência das oscilações espontâneas da PA para a VFSC, VR com inalação de CO_2 a 5% e hiperventilação não forçada, e ANV pela resposta da VFSC à estimulação visual.

RESULTADOS | Foram incluídos 10 doentes com DF e 10 controlos saudáveis emparelhados para sexo e idade. A avaliação com Doppler transcraniano revelou que a VR ao CO_2 estava significativamente afetada nos doentes com DF, principalmente na ACP, relativamente aos controlos (0,80±0,24 vs 1,12±0,24, p=0,015). Nos testes de ANV houve um menor aumento de VFSC nos homens com DF relativamente aos controlos (overshoot sistólico 15,00±2,93 vs 28,34±6,06, p=0,007 e overshoot médio 15,67±5,84 vs 31,62±6,17, p=0,009). A ARC foi semelhante entre os grupos.

CONCLUSÃO | Os doentes com DF de fenótipo clássico e ainda sem expressão clínica de DVC revelaram uma VR ao CO_2 significativamente afetada, e os de sexo masculino mostraram ter adicionalmente um pior desempenho no ANV, relativamente aos controlos. Assim, os nossos resultados apoiam a hipótese de a regulação microvascular estar afetada numa fase pré-sintomática da DVC na DF, e desta forma, o Doppler transcraniano dinâmico com testes de stress poder ser útil na monitorização deste atingimento e de eventuais respostas a intervenções terapêuticas no futuro.

CO.10 | Comparação de péptidos natriuréticos para a identificação de fibrilhação auricular em AVC isquémico

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INTRODUÇÃO | Cerca de um terço dos AVC isquémicos são criptogénicos segundo a classificação TOAST. É possível que a fibrilhação auricular (FA) paroxística seja responsável por uma fração destes eventos. Biomarcadores como o N-terminal do péptido natriurético cerebral (NT-proBNP) mostraram ser úteis na identificação de eventos cardioembólicos e de FA. Porém, o péptido natriurético auricular (ANP) pode ter uma maior acuidade que o NT-proBNP para o diagnóstico de FA dado que é produzido nas aurículas.

OBJETIVOS | Estabelecer qual dos biomarcadores, ANP ou NT-proBNP, tem maior acuidade para o diagnóstico de FA em doentes com AVC isquémico.

METODOLOGIA | Trata-se de um estudo observacional com recurso a uma coorte retrospetiva de doentes internados na unidade de AVC do Hospital de Santa Maria entre 08/2012 e 10/2013. Incluíram-se doentes com AVC isquémico agudo ou AIT e amostras de soro disponíveis no Biobanco. Excluíram-se doentes com TFG<30mL/min e amostras colhidas mais de 72h após o início dos sintomas. A etiologia dos eventos foi estabelecida com recurso à classificação TOAST. A análise estatística incluiu a determinação, análise e comparação de curvas ROC.

RESULTADOS | Obteve-se uma amostra de 204 doentes, 38,2% do sexo feminino e com uma mediana de idades de 65 anos. Destes, 36,8% tiveram eventos cardioembólicos, 18,6% cardioembólicos com FA e 37,3% criptogénicos. Para o diagnóstico de eventos cardioembólicos com FA versus não cardioembólicos, obteve-se uma curva ROC com AUC 0.83 (IC 95% 0.76-0.90) para NT-proBNP e 0.66 (IC 95% 0.56-0.75) para o ANP. Comparando eventos cardioembólicos com FA versus criptogénicos, o NT-proBNP mostrou uma AUC de 0.83 (IC 95% 0.75-0.90), e o ANP uma AUC de 0.62 (IC 95% 0.52-0.73).