

## Cardiac Biomarkers in Acute Stroke

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### Abstract

**Background:** Serum cardiac biomarkers are increased in cerebrovascular diseases. The aim of our study was to assess their levels according to the severity of cardiological and neurological conditions.

**Methods and results:** We recruited 552 acute ischaemic stroke (AS), 290 chronic cerebrovascular (CCVD) and 111 other neuropsychiatric diseases (OND) patients. Blood withdrawals were performed within 12-24 hours. Serial assessments were repeated at day 3 and 7.

At admission, high sensitive T Troponin (hs T Tro) and N-Terminal Pro-Brain Natriuretic Peptide II (NT-pro- BNP) levels were increased in AS and CCVD compared to OND (*inter-group variability*), especially in patients in class III/IV, C/D New York Heart Association and American Cardiology Association scales. Signs of acute myocardial infarction were observed in a minority of patients. No significant fluctuations were found within each group of patients at repeated measurement in one-week time (*intra-group unvariability*) at ANOVA repeated measures. However, *delta criterion* allowed identifying malignant cerebrovascular profile. ASPECTS scores were tendentially lower in patients in class III/IV New York Heart Association, C/D American Cardiological Association scales with stable or increased levels of NT-pro-BNP compared to those with 100% relative percentage decrease of such biomarker at day VII. Better clinical course and prognosis were observed in AS patients with at least 50% relative percentage decrease of NT-pro-BNP at day 7.

**Conclusions:** Although serum cardiac biomarkers may reflect more the chronicity rather than the acuity of ischaemic sufferance, *delta criterion* helps in differential diagnosis between acute versus chronic condition. NT-pro-BNP may be an early warning marker of either an adaptive or maladaptive response, with volume and pressure overload preceding hs T Tro rise and irreversible systemic, ischaemic damage. Moreover, it is reliable for assessing the severity of clinical conditions and the prognosis 279.

**Keywords:** Cardiac markers, Cerebrovascular diseases

### Introduction

In clinical practice, it is pivotal to identify useful parameters for prompt diagnosis, continuous monitoring, correct treatment, definite prognosis, safe discharge, scheduled follow up. Two cardiac biomarkers, high sensitive T Troponin (hs T Tro) and Brain Natriuretic Peptide (BNP), are commonly assessed in emergency department and for monitoring clinical conditions during hospitalization.

T Tro is a structural myocardial molecule. In myocardial necrosis, the entity of its release is a marker of the severity of acute coronary syndrome [1]. Its level predicts all-cause mortality [2-4], correlates with stroke severity, disability, increased brief and long-term mortality [5-11]. However, the dynamic relative and absolute changes are prognostically more significant than stable elevation in chronic conditions. National Academy of Clinical Biochemistry suggests using the *delta criterion* (changes greater than 20%) in sensitive assay

when the value is above 99<sup>th</sup> percentile [12,13].

BNP is synthesized and released by cardiomyocytes in response to cardiac haemodynamic stress with increased transmural wall tension (heart volume and pressure overload). Its level tends to be higher in female gender and increases by aging [14,15]. It is considered a marker of cardiac impairment, as in left ventricular dysfunction and cardiac heart failure [16-19]. N-Terminal Pro-Brain Natriuretic Peptide II (NT-pro-BNP) results from cleavage of the precursor molecule, namely pro-BNP. It is considered the best diagnostic and prognostic parameter in cardiac heart failure [20]. It is a strong predictor for coronary artery disease severity and correlates with left ventricular ejection fraction [21]. Low in-hospital reduction and high discharge level are independent markers for death or readmission after decompensated chronic heart failure [22,23]. Intensive care survivors had significantly lower NT-pro-BNP values than non-survivors [24]. This parameter predicts risk of stroke [25-29], its clinical and radi-

ological severity, recurrence and poor prognosis [30-37], cardioembolic genesis [38].

Both cardiovascular biomarkers are associated with increased risk of all-cause mortality [39-41].

The aim of our study was to evaluate hs T Tro and NT-pro-BNP levels in patients affected with acute stroke and/or chronic cerebrovascular conditions 313.

## Materials and Methods

Nine-hundred-fifty-three patients, 552 (57.9%) of which affected with acute ischaemic stroke (AS) (age 78.6 sd 11.5), 290 (30.4%) with chronic cerebrovascular (CCVD) (age 77.3 sd 8.7) and 111 (11.6%) with other neuropsychiatric diseases (OND), as psychoses,

epilepsies, minor traumas, (age 49.2 sd 15.4), were recruited in our Neurological Unit/Spoke Unit (Table 1). Blood withdrawals were performed within 12-24 hours after admission. Serial assessments were repeated at day 3 and 7. Results were analyzed in subgroups of patients according to the severity of heart and neurological dysfunction, evaluated by the CHAD2DS2VAsc, HAS BLED, New York Heart Association (NYHA), American Cardiology Association (ACA) scales, Simplified Pulmonary Embolism Severity Index (SPESI), Pulmonary Embolism Severity Index (PESI), Apache score, Glasgow Coma (GCS)/Outcome (GOS) scales, Hachinski and Modified Rankin Scale (MRS) scales. ECG, transthoracic and/or transesophageal echocardiography were performed within one-week time. We focalized our attention on the following echocardiographic parameters: ejection fraction (EF, normal range 60-80%), pulmonary arterial pressure

**Table 1:** Patients classification bases on their conditions.

	OND	CCVD	AS
<b>Number of patients</b>	111	290	552
<b>Age</b>	49.2 sd 15.4	77.3 sd 8.7	78.6 sd 11.5
<b>Males</b>	63 (56.8%)	165 (56.9%)	265 (48%)
<b>Females</b>	48 (43.2%)	125 (43.1%)	287 (52%)
<b>Male age</b>	51.1 sd 15.5	77.3 sd 8.7	75.4 sd 12.7
<b>Female age</b>	46.3 sd 16.1	75.8 sd 9.1	81 sd 9.7
<b>Past smokers</b>	31 (27.9%)	90 (31%)	204 (37%)
<b>Current smokers</b>	27 (24.3%)	23 (7.9%)	45 (8.2%)
<b>Potus</b>	21 (18.9%)	70 (24.1%)	121 (21.9%)
<b>Arterial Hypertension</b>	46 (41.4%)	244 (84.1%)	469 (85%)
<b>II type Diabetes</b>	6 (5.4%)	64 (22%)	149 (27%)
<b>Hypercholesterolemia (LDL &gt; 100 mg/dl)</b>	1 (0.9%)	122 (42.1%)	221 (40%)
<b>CHAD2VASC2</b>	1.2 sd 1.1	4.4 sd 1.5	5.9 sd 1.7
<b>HAS BLED</b>	0.9 sd 1	3.1 sd 1.1	3.9 sd 1.2
<b>Hachinski scale</b>	1.9 sd 2	7.3 sd 2.5	9.2 sd 2.6
<b>GCS at admission</b>	14.9 sd 0.3	14.1 sd 1.7	12.8 sd 2.7
<b>GCS at day 7</b>	14.9 sd 1.2	14.5 sd 0.9	13.5 sd 2.5
<b>GOS at day 7</b>	5 sd 0.1	4.5 sd 0.7	3.9 sd 0.9
<b>pre-stroke MRS</b>	0 sd 0.2	0.9 sd 1.3	1 sd 1.4
<b>MRS at day 7</b>	0 sd 0.2	1 sd 1.5	2.2 sd 1.8
<b>Previous ischaemic strokes</b>	0	38 (13.1%)	83 (15%)
<b>Lacunae</b>	0	290 (100%)	61 (11.1%)
<b>Significant stenosis or occlusion of major brain arteries (&gt; 50%)</b>	3 (2.7%)	96 (33.1%)	199 (36.1%)
<b>Significant kinking of major brain arteries (&lt; 60°)</b>	0%	20 (6.9%)	33 (6%)
<b>Significant stenosis or occlusion of major brain arteries (&gt; 50%), potentially related to AS</b>	0%	0%	61 (11.1%)
<b>Significant kinking of major brain arteries (&lt; 60°), potentially related to AS</b>	0%	0%	0%
<b>Class I/II NYHA, A/B ACA</b>	109 (98.2%)	184 (63.4%)	199 (36%)
<b>Class III/IV NYHA, C/D ACA</b>	2 (1.8%)	106 (36.6%)	353 (63.9%)
<b>Supraventricular extrasystolia</b>	30 (27%)	61 (21%)	94 (17%)
<b>Ventricular extrasystolia</b>	20 (18%)	61 (21%)	94 (17%)
<b>Blocks of branches</b>	12 (10.8%)	61 (21%)	110 (19.9%)
<b>Atrioventricular blocks</b>	2 (1.8%)	14 (4.8%)	22 (4%)
<b>Atrial fibrillation</b>	0%	38 (13.1%)	166 (30%)
<b>Myocardial necrosis at ECG</b>	3 (2.7%)	3 (1%)	20 (3.6%)
<b>Myocardial necrosis at echocardiography</b>	5 (4.5%)	14 (4.8%)	40 (7.2%)

(PAP, normal < 25 mmHg), atrial dimension (AD, normal range 3.3 sd 0.5 cm). All patients underwent Computerized Tomography and/or Magnetic Resonance Imaging at admission, after 24 hours and, if necessary, repeated.

Cardiac biomarkers were detected according to standard methods. Serum hs T Tro and NT-pro-BNP II levels were measured by electrochemiluminescence immunoassay with biotinylated monoclonal anti-mouse-T Tro and anti-mouse-NT-pro-BNP-specific antibodies labeled with ruthenium, which formed a sandwich complex. After addition of streptavidin-coated microparticles, it bound to solid phase. The microparticles were aspirated and magnetically captured by an electrode, while unbound particles were removed. Voltage induced chemoluminescence was revealed by Cobas analyzer (Elecys and Cobas, Roche). The cut off value to rule out myocardial infarction was < 15 pg/ml for hs T Tro. Normal range value of NT-pro-BNP were 0-125 pg/ml.

Statistical analysis was performed by unpaired T test, ANOVA repeated measures, for standard description of baseline characteristics and differences among the studied groups, by Pearson correlation test and regression analysis, for identification of association among examined parameters. Moreover, delta criterion was applied, considering differences of at least 20% for hs T Tro and 50% for NT-pro-BNP 345.

## Results

Increased hs T Tro and NT-pro-BNP were detected in AS (hs T Tro: 59.6 sd 356.3 pg/ml, p 0.02; NT-pro-BNP: 3103.6 sd 5772.6 pg/ml, p 0.01) and CCVD (hs T Tro: 28.1 sd 33.6 pg/ml, p 0.03; NT-pro-BNP: 1031.6 sd 2462.2 pg/ml, p 0.03) compared to OND (hs T Tro: 6.8 sd 4.5 pg/ml; NT-pro-BNP: 124.7 sd 245.5 pg/ml) at T test (*intergroup variability*) (Figure 1). Levels above normal values of hs T Tro were present in 373 (67.5%) AS, 169 (58.2%) CCVD, 7 (6.3%) OND, of NT-pro-BNP in 477 (86.4%) AS, 220 (75.8%) CCVD, 32 (28.8%) OND.

Three-hundred-fifty-three (63.9%) AS, 106 (36.6%) CCVD and two (1.8%) OND were classified in class III/IV NYHA, C/D ACA (Table 1). Significant differences were found between patients in class I/II, A/B compared to class III/IV, C/D NYHA and ACA scales in AS (hs T Tro 18.9 sd 27.6 vs. 79.7 sd 380.7 pg/ml, p 0.001; NT-pro-BNP 241.8 sd 238.5 vs. 7202.1 sd 4821.5 pg/ml, p 0.01) (Figure 2).

Moreover, the subgroup of AS with CCVD had higher levels compared to AS without CCVD (hs T Tro: 50.1 sd 117.9 vs. 17.6 sd 27.7 pg/ml, p 0.01; NT-pro-BNP 3609.5 sd 6121.7 vs. 1092.1 sd 3449.8 pg/ml, p 0.03) (Figure 3).

Signs of acute myocardial necrosis were observed in a minority of patients, 3 (2.7%) OND, 3 (1%) CCVD, 20 (3.6%) AS at electrocardiograms, 5 (4.5%) OND, 14 (4.8%) CCVD, 40 (7.2%) AS at echocardiograms.

Supraventricular extrasystolia was present in 30 (27%) OND, 61 (21%) CCVD, 94 (17%) AS, ventricular extrasystolia in 20 (18%) OND, 61 (21%) CCVD, 94 (17%) AS, blocks of branches in 12 (10.8%) OND, 61 (21%) CCVD, 110 (19.9%) AS, atrioventricular blocks in 2 (1.8%) OND, 14 (4.8%) CCVD, 22 (4%) AS, atrial fibrillation in 38 (13.1%) CCVD, 166 (30%) AS, minor valvular dysfunctions in 28 (25.2%) OND, 159 (54.8%) CCVD, 267 (48.4%) AS, moderate-severe valvular cardi-

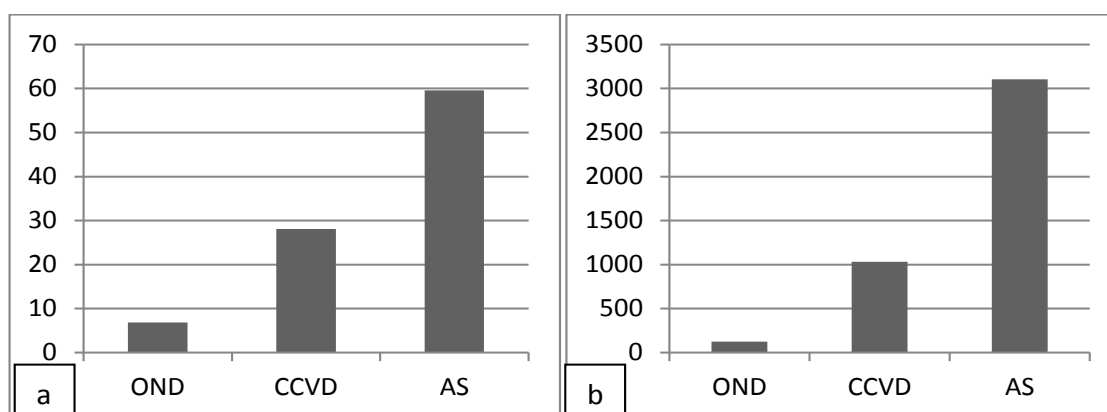


Figure 1: Levels of hs T Tro (a) and NT-pro-BNP (b) in OND, CCVD and AS patients at admission.

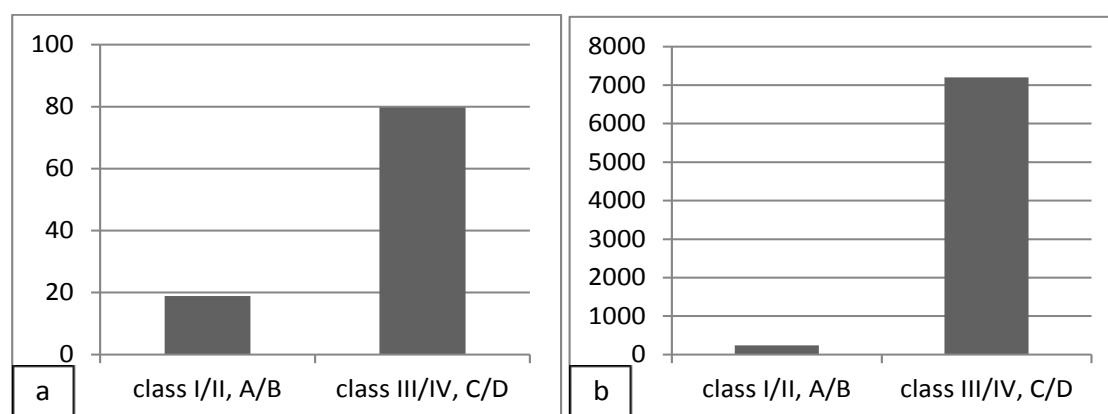


Figure 2: Levels of hs T Tro (a) and NT-pro-BNP (b) in class I/II NYHA, A/B ACA and class III/IV NYHA, C/D ACA AS patients at admission.

opathy in 44 (15.2%) CCVD, 144 (26.1%) AS (Table 1). The reliability of cardiac biomarkers concerning myocardial infarction is shown in Table 2. Significant correlation was observed between levels of NT-pro-BNP and severity of cardiac dysfunction evaluated by NYHA and ACA scales, the severity of which were scored in the range of 1 to 4 (r 0.50).

Serial assessment did not show significant fluctuations within each groups of patients at day 3 and 7 compared to admission (*intra-group unvariability*) (Figure 4) and at different time lag in bounce

backs (preliminary data, not shown) at ANOVA repeated measures.

Overall, according to the delta criterion, significant relative decrease > 20% of hs T Tro was found in CCVD (- 31.16%) (Figure 5a). Significant relative percentage decreases > 50% of NT-pro-BNP were observed in OND (-124.2%), in CCVD (-58.04%) and in AS (-91.17%) (Figure 5b). Relative percentage decreases > 20% of hs T Tro were present in 28 (25.2%) OND, 85 (29.3%) CCVD, 186 (33.7%) AS. Relative percentage decreases > 50% of NT-PBNP were detected in 58 (52.3%) OND, 103 (35.5%) CCVD, 235 (42.6%) AS. No significant

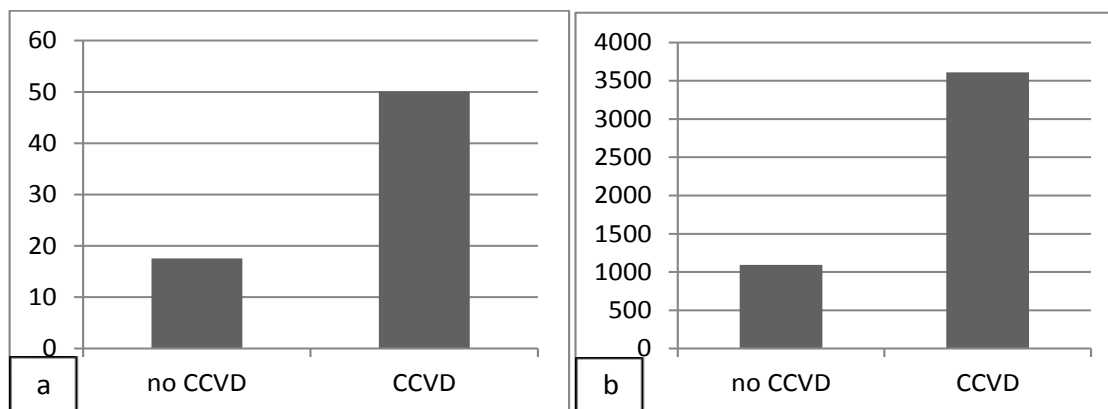


Figure 3: Levels of hs T Tro (a) and NT-pro-BNP (b) in AS patients without or with CCVD at admission.

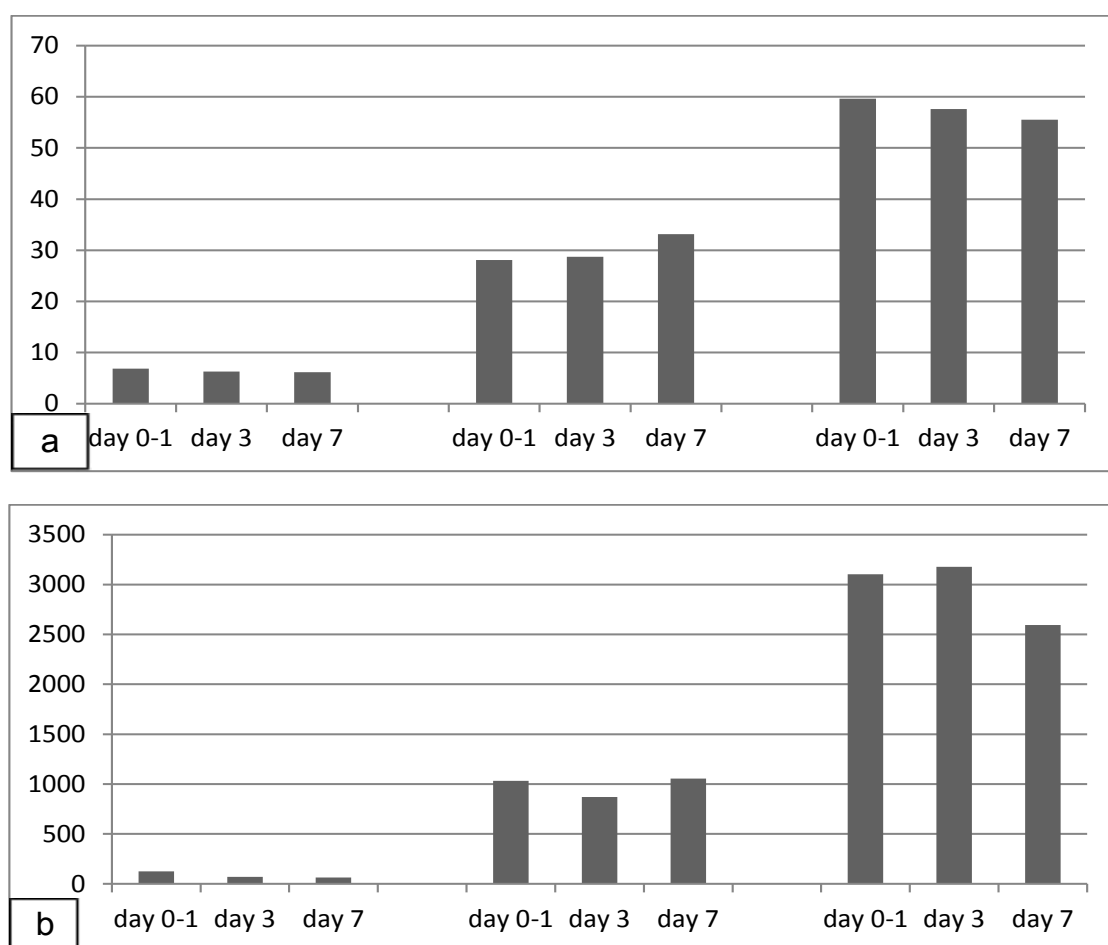


Figure 4: Serial assessment of hs T Tro (a) and NT-pro-BNP (b) at day 0-1, 3 and 7 in patients affected with OND (left columns), CCVD (columns at center), AS (right columns).

**Table 2:** The reliability of cardiac biomarkers concerning myocardial infarction.

	hs T Tro	NT-pro-BNP
<b>Sensibility</b>	82.40%	92%
<b>Specificity</b>	97.60%	75%
<b>Positive Predictive Value</b>	91.30%	61.80%
<b>Negative Predictive Value</b>	90.20%	84.60%
<b>Accuracy</b>	90.60%	78.90%

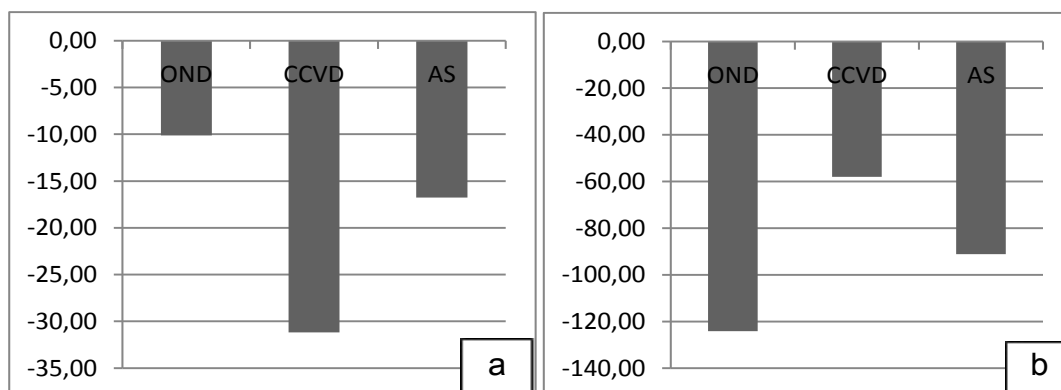
**Table 3:** Significant differences were present between AS with relative decrease of at least 50% in NT-pro-BNP levels compared with AS without significant changes.

	no NT-pro-BNP changes	at least 50% decrease of NT-pro-BNP
<b>I GCS</b>	11.9 sd 2.9	12.6 sd 2.7
<b>VII GCS</b>	12.8 sd 2.6	13.6 sd 2.1
<b>GOS</b>	3.5 sd 0.8	3.8 sd 0.8
<b>pre-stroke MRS</b>	1.34 sd 1.56	1 sd 1.46
<b>VII MRS</b>	3.1 sd 1.6	2.6 sd 1.7
<b>Hachinski scale</b>	10.4 sd 2.1	9.9 sd 2
<b>HASBLED</b>	4.4 sd 1	4.2 sd 1

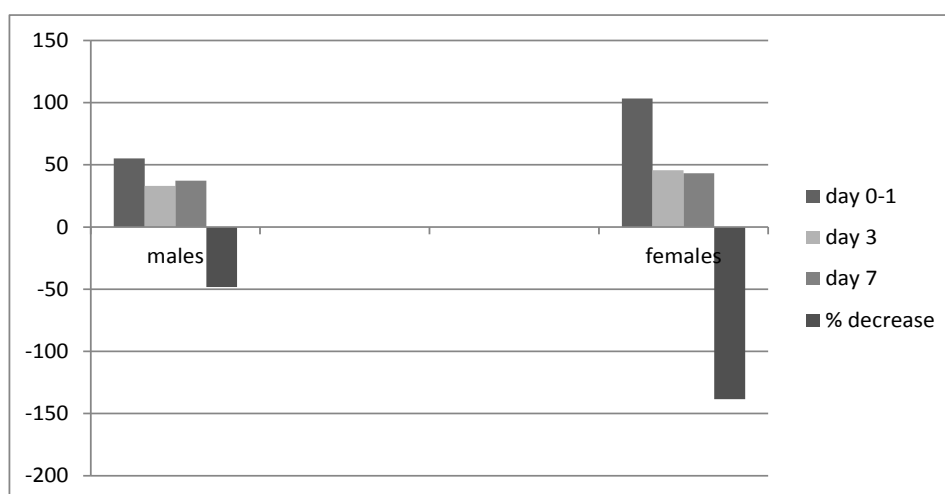
relative percentage changes were revealed in 65 (58.6%) OND, 157 (54.1%) CCVD, 243 (44%) AS concerning hs T Tro, 44 (39.6%) OND, 156 (53.8%) CCVD, 248 (44.9%) AS concerning NT-pro-BNP.

Significant differences were present between AS with relative decrease of at least 50% in NT-pro-BNP levels compared with AS without significant changing of such marker regarding GCS (12.6 sd 2.7 vs. 11.9 sd 2.9, p 0.02), pre-stroke MRS (1 sd 1.46 vs. 1.34 sd 1.56, p 0.03), Hachinski scale (9.9 sd 2 vs. 10.4 sd 2.1, p 0.01), HAS (4.2 sd 1 vs. 4.4 sd 1, p 0.02) at admission, GCS (13.6 sd 2.1 vs. 12.8 sd 2.6, p 0.0004), GOS (3.8 sd 0.8 vs. 3.5 sd 0.8, p 0.0001), MRS (2.6 sd 1.7 vs. 3.1 sd 1.6, p 0.0006) at day 7 (Table 3). The highest levels of hs T Tro were detected in class III/IV, C/D patients with at least 50% relative increase compared to those with at least 50% relative decrease of NT-Pro-BNP at day VII. These patients had the lowest GCS at admission, as well as the lowest GCS and highest MRS at day VII.

In class 0/I OND, a significant reduction of NT-pro-BNP levels was already detected at day 3 (38.7 sd 34.6 vs. 77.2 sd 71.3, p 0.0001), especially in females, compared to males (females 45.7 sd 30.4 vs. 103.3 sd 74.2, p 0.0002; males 33.1 sd 37.1 vs. 55.2 sd 61.6, p 0.06). This finding was confirmed at day 7 (40.3 sd 54.3 vs. 77.2 sd 71.3, p 0.01; females 43.3 sd 28.3 vs. 103.3 sd 74.2, p 0.007; males 37.2 sd 73 vs. 55.2 sd 61.6, p 0.08) (Figure 6). Any stressful event, diagnostic procedures included, were responsible of fluctuations of such marker.



**Figure 5:** Relative percentage decreases hs T Tro (a) and NT-pro-BNP (b) in OND, CCVD and AS patients at day 7.



**Figure 6:** Serial assessment of NT-pro-BNP at day 0-1, 3 and 7 in male (left) and female (right) patients affected with OND and respective relative percentage decreases at day 7.

Significant differences were observed in AD between OND, CCVD and AS (OND 3.5 sd 0.6 cm vs. CCVD 4.2 sd 0.6 cm, p 0.03; OND 3.5 sd 0.6 cm vs. AS 4.8 sd 4.3 cm, p 0.01) (Figure 7). The most significant correlations were present between hs T Tro and EF (r -0.22), AD (r 0.28), PAP (r 0.23), between NT-pro-BNP and EF (r -0.24), AD (r 0.25), PAP (r 0.48) in CCVD, between NT-pro-BNP and EF (r -0.34), PAP (r 0.47) in AS.

Lacunae were present in all CCVD and in 61 (11.1%) AS. Signs of previous ischaemic strokes were evident in 38 (13.1%) CCVD and 83 (15%) AS. Acute infarcts were in the territory of anterior circulation in 320 (58%) AS, in vertebro-basilar areas in 110 (19.9%) AS. Haemorrhagic infarction occurred in 22 (4%) AS. Other 122 (22.1%) AS were considered lacunar. No significant differences of cardiac biomarkers were related to the region of the cerebral infarction (Internal Carotid Artery, Middle Cerebral Artery, Anterior Cerebral Artery AS: hs T Tro 73.4 sd 430.2 pg/ml, NT-pro-BNP 3898.6 sd 6648.4 pg/ml; Vertebro-Basilar AS: hs T Tro 60 sd 153.5 pg/ml; NT-pro-BNP: 3607.9 sd 6143.7 pg/ml, p ns). This was confirmed in subgroups' analysis among cardiac biomarkers in fronto-parietal (hs T Tro 24.93

sd 19.37 pg/ml; NT-pro-BNP 1717.1 sd 1996.4 pg/ml), temporo-insular (hs T Tro 23.9 sd 15.1 pg/ml; NT-pro-BNP 2581 sd 4166.1 pg/ml), capsulo-nuclear (hs T Tro 27.73 sd 27.27 pg/ml; NT-pro-BNP 2022.4 sd 2435.5 pg/ml), occipital (hs T Tro 41.68 sd 42.57 pg/ml; NT-pro-BNP 2398.8 sd 2198.4 pg/ml), cerebellar-brainstem (hs T Tro 30.6 sd 26.4 pg/ml; NT-pro-BNP 2080.8 sd 2771.9 pg/ml) AS (Figure 8). Their levels as the extension of cerebral ischaemia were related to the overall severity of neurocardiological dysfunction, responsible of diffuse hypoxic encephalopathy in severe cases. In patients with early neuroradiological signs of cerebral ischaemia at admission, ASPECTS scores were tendentially lower in patients with stable or increased levels of NT-pro-BNP compared to those with at least 100% relative decrease of NT-pro-BNP at day VII (class I/II NYHA, A/B ACA patients 5.33 sd 1.56 vs. 5.83 sd 1.6, p ns; class III/IV NYHA, C/D ACA 4.25 sd 1.71 vs. 5.03 sd 1.66, p 0.07) (Figure 9). In the latter, significant correlations were found between ASPECTS, GCS (r 0.47) at admission, GCS (r 0.30), MRS (r -0.20), hs T Tro (-0.58) at day VII 1192.

**Discussion**

Cardiac markers are increased in cerebrovascular conditions, particularly in AS in class III/IV, C/D NYHA and ACA scales and in the contest of chronic cerebrovascular disease (CCVD), compared to other neurological diseases (OND) (inter-group variability). No significant fluctuations were found within each group of patients at repeated measurements in one-week time (intra-group unvariability) and at different time lag in bounce backs (preliminary data). However, significant absolute and relative changes of such parameters are pivotal for early detection of sudden acuity or worsening of chronicity. Moreover, their decreases are associated with better outcomes while their increases point out a malignant prognosis.

NYHA scale allows a quick assessment of the severity of cardioclogical conditions. Together with cardiac biomarkers speed up diagnostic iter for appropriate emergency treatments. According to cardiologic criteria, since cardiac biomarkers reveal myocardial injury, independently on the etiopathogenetic cause, their elevation is not sufficient for a definite diagnosis of acute coronary syndrome. At least one of the following clinical criteria has to be present: symptoms of ischemia, electrocardiogram changes (new ST-T changes or

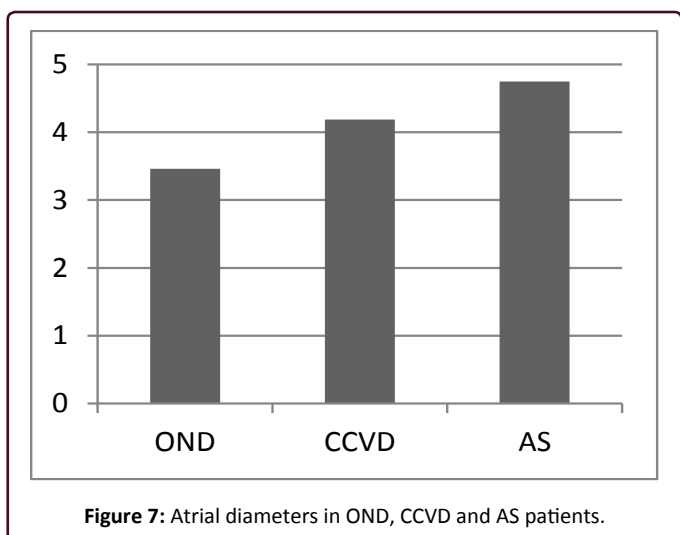


Figure 7: Atrial diameters in OND, CCVD and AS patients.

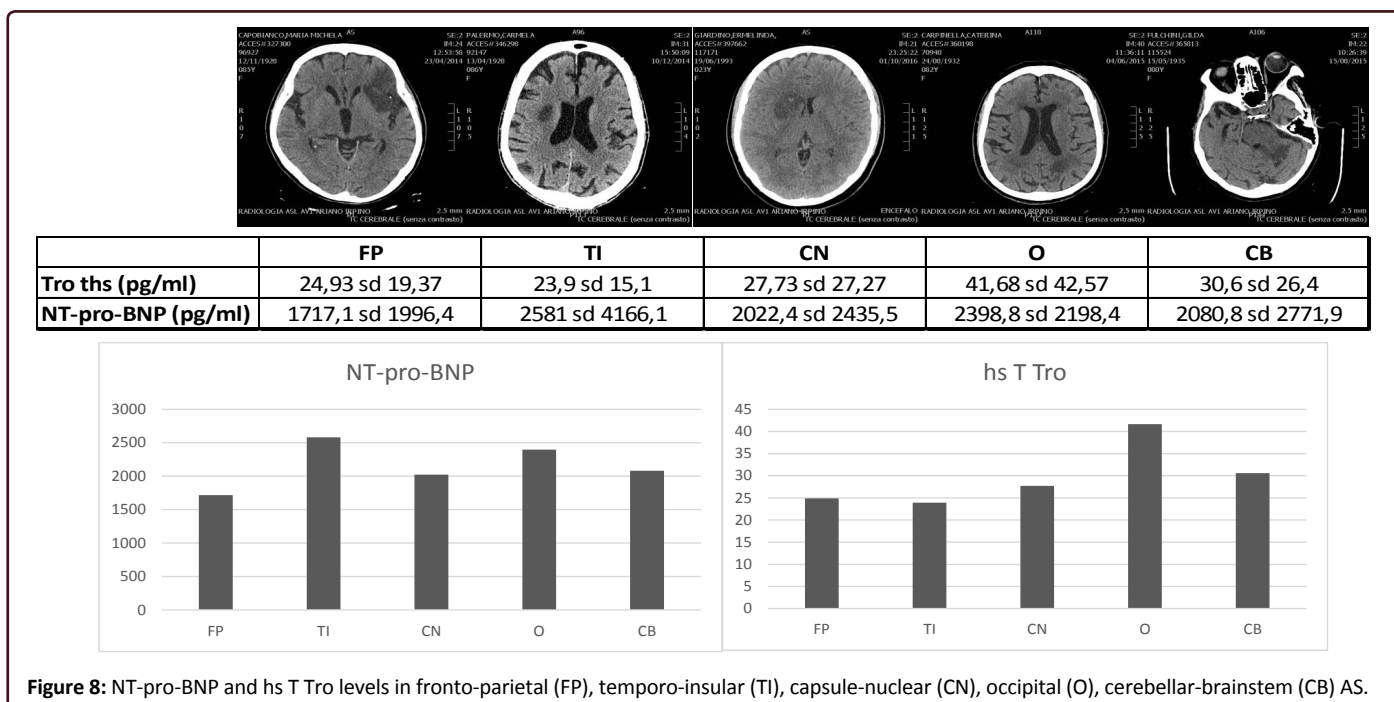
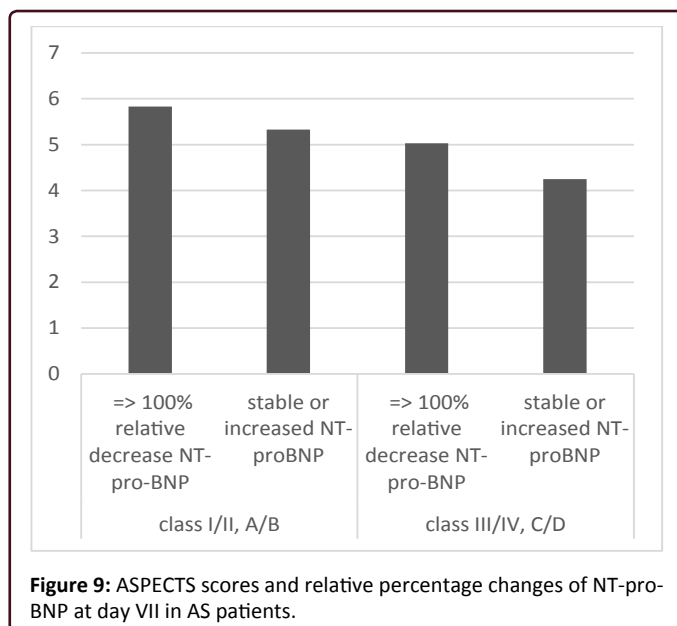


Figure 8: NT-pro-BNP and hs T Tro levels in fronto-parietal (FP), temporo-insular (TI), capsule-nuclear (CN), occipital (O), cerebellar-brainstem (CB) AS.



Left Bundle Branch Block, new Q waves), imaging evidence, such as a new regional wall motion abnormality, new loss of viable myocardium on the echocardiogram or intracoronary thrombus at coronarography [42]. We found significant ECG/echocardiographic acute ischaemic signs in a minority of our patients. Therefore, we highlight the value of cardiac biomarkers for risk evaluation and for monitoring clinical conditions. Moreover, their levels predict the severity at ACA scale.

However, in real-world practice, comorbidities are frequent, reduce penumbra and collaterals, account for increased levels of both T Tro and NT-pro-BNP. In Dallas Heart Study, up to 40% of patients have troponin levels in the range of myocardial infarction [43]. Association with age, male gender, trauma, burns, inflammation, hypertension, diabetes, heart failure, cerebrovascular accidents, pulmonary emboli, renal impairment is reported. More than 90% of patients with stable coronary artery disease, without heart failure, have levels of T Tro within the measuring range [44]. Nonetheless, the utility of delta criterion to distinguish acute from chronic conditions is undeniable. In this regard, we observe that relative percentage decreases ought to be considered together with absolute levels and changes, especially in critical conditions (e.g. the relative percentage decrease has a different meaning if the absolute value is in the range of thousand or ten picograms). Prognostic sensibility of NT-pro-BNP seems to be even higher than that of T Tro [45,46]. Among cardiac biomarkers, NT-pro-BNP has the features of an ideal biomarker, since it is released quickly for early diagnosis, it is persistent for a reasonable amount of time to allow a diagnostic window (half-life 90-120 minutes) and can be quantified accurately and economically, reflecting changes in both the patient's status and prognosis [47]. NT-pro-BNP levels resulted to be a stronger prognostic marker than ECG and its dosage has been proposed as first test for cardiovascular stratification instead of ECG [48]. A single measurement of BNP is pivotal for urgent decision making, although continuous monitoring may better define the prognosis [49]. Its shorter half-life (20 minutes) may limit its utility compared NT-pro-BNP. The latter is strongly associated with myocardial infarction, microsize one included, and fatal outcomes [50]. It may allow a quick risk stratification in emergency. Clinical practice guidelines on Heart Failure consider natriuretic peptides in class I of recommendation, level A of evidence for diagnosis and prognosis. Natriuretic peptide screening and guided therapy may prevent heart failure, reducing cardiovascular death and death by any cause [51]. A meta-analysis reported that NT-pro-BNP concentration strongly predicts first-onset heart

failure and risk of coronary heart disease and stroke [52]. Although the levels of high sensitive troponins seem to be related to the entity and rapidity of ischaemic process, their short half-lives may account for low positive predictive value, although higher their levels are, worst the outcomes. They seem to be more helpful for ruling out than ruling in acute myocardial infarction and no difference was reported in incidence of subsequent acute events or death from cardiovascular causes [53]. In severe acute stroke, a diffuse myocardial suffering may be present, both for a chronic primary or secondary coronary hypoperfusion and stroke-related hyper-contracted state, responsible of coagulative myocytolysis and contraction band necrosis [54]. However, a misleading relative decline of high sensitive troponin levels may be observed because of reduced myocardial contractions and haemodilution in severe, end stage heart failure.

Our finding of significant fluctuations of NT-pro-BNP in class 0/I OND patients suggests that the burden may be wider than expected as well as the reversibility of physiological response versus a shift toward pathological dysfunctions. Any stressful event may interfere with physiological circulation, because of a prevalence of sympathetic over parasympathic activity. NT-pro-BNP may be a warning marker of either an adaptive or maladaptive response. It is reported that the risk of cardiovascular disease in individuals with relatively low levels of NT-pro-BNP (55-124 pg/ml) was 1,9-fold higher than in those with the lowest levels (< 55 pg/ml) [55], independently of conventional risk factors [55,56]. Patients with elevated natriuretic peptides without heart failure may have an increased risk of developing symptomatic heart failure [57]. Indeed, NT-pro-BNP is the most sensible and useful parameter, reflecting atrial overload and myocardial spreading depression. These may stand for physiological preconditioning or evolve toward subtle, critical ischaemia. The shift toward irreversibility depends on ejection fraction, peripheral resistances, compliance, strictly linked and further exacerbated by cerebral anoxic-ischaemic damage. The compensatory response, reducing arterial pressure and inducing natriuresis and diuresis, may become pathological, triggering a cascade of events, culminating in the Virchow triad (reduced flow, endothelial damage, increased coagulability), with subsequent elevated risk of ischaemic suffering. This may be signaled by the rise of T Tro, before the appearance of electrocardiographic signs. Longer the hypoperfusion, worst and irreversible the cardiological and cerebral outcomes are. *In vitro*, cerebral tissue is even more vulnerable than cardiac one [58]. *In vivo*, within few seconds of cerebral ischaemia, electroencephalogram activity ceases, as an energy sparing response [59,60]. The impairment of respiratory chain, anoxic depolarization and spreading depression extend from the ischemic core to the ischaemic penumbra; no reflow phenomenon and/or haemorrhagic infarction may occur, especially in decompensated heart failure. Either in acute or in chronic cerebrovascular conditions, a cranio-caudal cascade may contribute to "neurogenic stunned myocardium", which worsen cardiac and cerebral perfusion. Further studies are needed on the relation between cardiac biomarkers and entity of cerebral damage. Our results highlight that even late may still be brain in all AS, class III/IV, C/D NYHA, ACA included. However, poor collaterals, decreased perfusion, increased diffusion, retrograde venous leakage may account for futile recanalization and increase the risk of haemorrhagic complications.

Moreover, In AS in the context of CCVD, the concomitant presence of chronic myocardial ischaemic suffering further increases the mismatch between diffusion and perfusion with subsequent risk of cerebral ischaemic core enlargement, oedema formation, mass effect on brainstem, diffuse anoxic ischaemic encephalopathy. Although some authors observed an increased risk of cardiac arrhythmia and death in AS with insular involvement [61], we did not find differences in cardiac biomarkers between insular and other AS. However, we do not exclude that an early and persistent rise of

cardiac biomarkers in AS in cortical-subcortical encephalic regions, as insula, diencephalon and brainstem, may predict a faster necrotic evolution and account for malignant dysautonomia. Moreover, the higher risk of stroke in patients suffering from sleep apnoea [62] suggests that transient or persistent lacunar, ischaemic sufferance may predispose to more severe ischaemic events, hinder the recovery and worsen the outcomes in vertebro-basilar AS, when respiratory centers in brainstem are early involved. Indeed, an association of sleep apnoea with clinically silent microvascular brain tissue changes in general population and in AS and between sleep disordered breathing and brainstem infarction are reported 1249 [63-65].

## Conclusion

NT-pro-BNP and hs T Tro are pivotal for a prompt assessment of circulatory condition for the most appropriate treatment, directed to widen the therapeutic window and limit the costs related to invalidating outcomes. While the former is a sign of functional alteration, the latter represents already a structural damage. Although serum cardiac biomarkers may reflect more the chronicity rather than the acuity of ischaemic sufferance, delta criterion helps in differential diagnosis between acute versus chronic condition. Since apparently physiological conditions may evolve to subtle or overt pathological conditions, parallel haematological and urinary parameters, together with more sophisticated electrophysiological and neuroradiological techniques, may help in defining the burden and lesional load and establish the criteria for rational procedures. Further studies are needed for better defining the therapeutical window in AS patients suffering from heart failure, decision making concerning the strategy of “scoop and run” to mechanical thrombectomy or “stay and play” with plasminogen activators and/or other pharmacological agents 157 TOT 3270.

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