

ORIGINAL ARTICLES

NT-proBNP levels and QT changes in acute ischemic stroke

¹Ayca Acikalin MD, ¹Salim Satar MD, ⁴Onur Akpınar MD, ²Caglar Emre Cagliyan MD, ⁵Mustafa Sahan MD, ⁶Ferhat Icme MD, ¹Muge Gulen MD, ³Mehmet Yildiz MD

Department of ¹Emergency Medicine, ²Cardiology and ³Neurology, Adana Numune Education and Research Hospital, Department of Emergency Medicine, Adana; ⁴Department of Cardiology, Adana BSK Metropark Hospital, Adana; ⁵Department of Emergency Medicine, Elazig Education and Research Hospital, Elazig; ⁶Department of Emergency Medicine, Ankara Atatürk Education and Research Hospital, Ankara, Turkey

Abstract

Background: In literature, electrocardiographic (ECG) changes and the increase in the levels of the natriuretic peptide are shown to occur in patients having acute ischemic stroke. We aimed to investigate the association between ECG alterations and NT pro B-type natriuretic peptide (NT-proBNP) values in patients having acute ischemic stroke with no known cardiac pathology. **Methods:** The patients who admitted to the emergency service with acute ischemic stroke were enrolled in the study. Their ECGs were recorded and serum samples were obtained as soon as they arrived into the emergency service. The plasma NT-proBNP levels were measured by electrochemiluminescence method. Maximum QT interval, QT dispersion (QTd), corrected QT and corrected QTd (cQT and cQTd) was calculated, for each ECG. The patients were evaluated according to the Glasgow Coma Scale (GCS) and National Institutes of Health Stroke Scale (NIHSS). **Results:** A total of 50 consecutive patients were evaluated. QT intervals for 4 patients (8%) and cQT intervals for 29 patients (58%) were above 440 ms and 11 patients (22%) had QTd values above 50ms and 17 (34%) had cQTd values above 50 ms. The NT-proBNP levels had a negative correlation with the GCS ($p=0.001$, $r= -0.461$) and a positive correlation with the NIHSS, cQT, QTd and cQTd ($p=0.001$, $r=0.444$, $p=0.000$, $r=0.494$, $p=0.016$, $r=0.338$ $p=0.011$, $r=0.355$, respectively).

Conclusions: The NT-proBNP levels in the ischemic stroke patients with no known cardiac pathology were markedly increased, and this increase was found to be associated with the GCS, NIHSS, cQT, QTd and the cQTd interval.

INTRODUCTION

Stroke is an important health problem that may lead to serious disabilities or even to death. The prevalence of stroke in our country is around 175/100,000 and an average of 120,000 new cases per annum is being admitted to the emergency services.¹ Ischemic strokes form 85% of all the strokes and are well known to be closely associated with cardiac thromboembolic events and atherosclerosis.

Electrocardiographic (ECG) changes including ST segment and T alterations, prolongation of the QT interval and formation of pathological Q waves are known to occur in patients having acute ischemic stroke.²⁻⁴ It is known that cardiac

disorders such as atrial fibrillation and acute myocardial infarction may be associated with ischemic strokes. In addition, ischemic strokes may cause the ECG alterations and/or myocardial damage by using non-ischemic mechanism in patients without cardiac pathology. And, it is well known that these changes in the ECG are associated with early mortalities.²⁻⁶

The increase in the levels of the natriuretic peptide during the acute phase of the stroke and its association with early mortality has been reported.⁷ However, information about the NT pro B-type natriuretic peptide (NT-proBNP) during the cerebrovascular events is limited. In this study, we aimed to investigate the association between

QT changes in ECG and NT-proBNP values in patients having acute ischemic stroke with no known cardiac pathology.

METHODS

The study group was composed of 50 consecutive patients who applied to the emergency service with acute ischemic stroke and were hospitalized within the intensive care unit (ICU) of the Neurology Department. The followings were excluded from the study: (1) Patients who had cardiogenic shock and/or who received cardiopulmonary resuscitation (CPR); (2) Patients who had documented coronary arterial disease or heart failure; (3) Patients with abnormal troponin values; (4) Patients who presented Q wave abnormalities in their ECGs; (5) Patients who presented bundle branch blocks or atrial flutter/fibrillation in their ECGs; (6) All of the patients had undergone echocardiography and patients with any echocardiographic abnormality were excluded from the study; (7) Patients who were unable to or not willing to give a written consent for the study.

All of the patients were examined and the diagnoses of stroke were confirmed by cerebral computer tomography (CT) and consultation from the Neurology Department. Their ECGs were recorded as soon as they arrived into the emergency service and serum samples were obtained for the investigation of the CK-MB, troponin T and NT-proBNP. Following a detailed neurologic examination the consciousness of the patients were evaluated according to the Glasgow Coma Scale (GCS) and National Institutes of Health Stroke Scale (NIHSS). The patients having a score between 0-6 according to the NIHSS were accepted to have a mild stroke, the ones having a score between 7 and 15 were classified to have a moderate stroke and the ones having a score of 16 to 38 were considered to have a serious stroke.^{8,9}

Following the necessary primary medical therapy in the emergency service, the patients were transferred to the ICU of the Neurology Department. The patients were given standard medical therapy that is accepted worldwide. The mortality rate for all the patients during their stay in the hospital was recorded.

Estimation of the total infarction volume: The total volume of the infarction areas that were present in the CT scans were estimated by multiplying these areas by the thickness (2mm) and adding them together.

Electrocardiographic analysis: A cardiologist who was blinded to the clinical diagnosis of the patients evaluated the ECG manually. The interval between the beginnings of the Q wave until the point where the T wave met with the isoelectric line was measured as the QT interval in terms of milliseconds. The Bazett formula ($QT/\sqrt{R-R}$) was used to calculate the corrected QT (cQT) interval in accordance with the heart rate. The difference between the longest QT interval and the shortest QT interval gave us the QT dispersion (QTd). The corrected QTd (cQTd) was obtained by the difference between the longest QTd and the shortest QTd. Corrected QT values that were above 440ms and QT dispersion values that were above 50ms were accepted to be abnormal.

Laboratory parameters: The measurements of troponin T and the CK-MB levels were performed by electrochemiluminescence method by using the Elecsys-2010 analyzer. The plasma NT-proBNP levels were measured by electrochemiluminescence method by using the Elecsys-2010 analyzer and the Roche Diagnostics' NT-proBNP kit.

Statistical analysis: SPSS 11.0 program was used for the statistical evaluation. The parametric data have been presented as mean and standard deviation values whereas the nonparametric data have been presented as frequencies. Parametric data among the demographic parameters were evaluated by the Student's *t* test and the nonparametric ones were evaluated by the Chi-square test. When the compared data were evaluated by the correlation analysis we used the multivariate regression analysis in order to estimate the independent risk factors.

RESULTS

The average age of the study group patients which consisted of 23 males and 27 females was 66.4 ± 12.7 (36-88) years. The lowest and highest GCS were 8 and 15 with the average of 13.1 ± 2.3 . The lowest and highest NIHSS scores were 0 and 30, with the average of 9.8 ± 7.8 (Table 1). Overall 28% of patients had abnormalities of ECG.

The NT-proBNP values were 1322.8 ± 2003.5 (range; 29.9-8604.0, median; 489.5). The average stay in the hospital was 11.2 ± 6.4 (0-38) days. QT intervals for 4 patients (8%) and cQT intervals for 29 patients (58%) were above 440 ms. Eleven patients (22%) had QTd values above 50ms and 17 (34%) had cQTd values above 50 ms (Figure 1).

Table 1: Baseline clinical characteristics

	Mean \pm SD	LL-UL	Median
Age (years)	66.4 \pm 12.7	36-88	68
Sex (M/F)	23/27	-	-
GCS	13.1 \pm 2.3	8-15	14
NIHSS	9.8 \pm 7.8	0-30	7
Total infarct volume (mm ³)	31977.3 \pm 54455.4	234 - 200960	3450
CKMB (ng/ml)	5.0 \pm 6.5	0.8 - 46.0	3.7
NT-proBNP (pg/ml)	1322.8 \pm 2003.5	29.9 - 8604.0	489.5
Hospitalization (day)	11.2 \pm 6.4	0 - 38	10
Pulse (/min)	79.8 \pm 16.4	52 - 120	74
PR duration (ms)	185.6 \pm 31.3	80 - 280	180
QT (ms)	388.8 \pm 40.0	320 - 480	400
cQT (ms)	443.5 \pm 38.0	360 - 529	445
QTd (ms)	42.4 \pm 16.0	20 - 80	40
cQTd (ms)	49.0 \pm 20.0	20 - 103	45.2

SD: Standard Deviation, LL: Lower Limit, UL: Upper Limit, GCS; Glasgow Coma Scale, NIHSS; National Institutes of Health Stroke Scale, CKMB; Creatine Kinase MB, NT-proBNP; NT pro B-type natriuretic peptide, QT; QT duration, cQT; corrected QT duration, QTd; QT dispersion duration, cQTd; corrected QT dispersion duration.

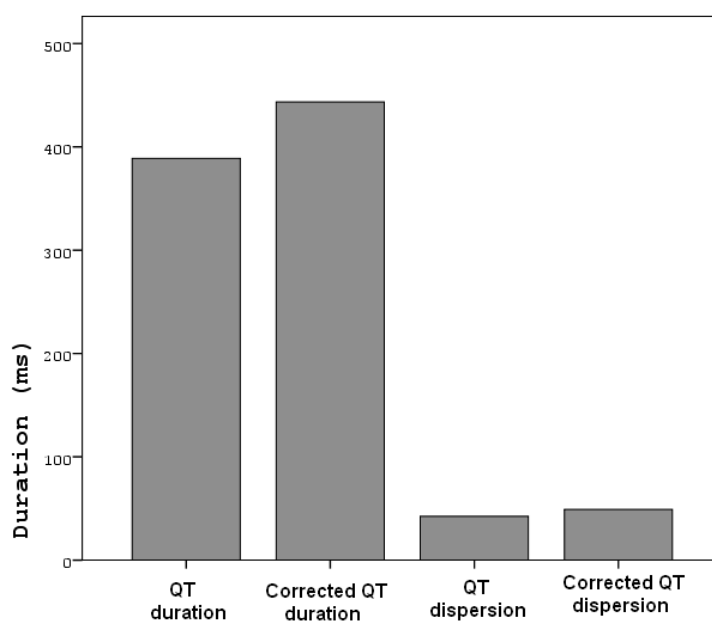


Figure 1. All of QT parameters' mean values.

Table 2: Baseline clinical characteristics of mild, moderate and severe stroke patients (according to NIHSS)

Group (According to NIHSS)	Mild stroke (Average \pm SD)	Moderate stroke (Average \pm SD)	Severe stroke (Average \pm SD)
Age (years)	65.2 \pm 13.1	69.3 \pm 8.7	64.0 \pm 17.4
Sex (M/F)	10/12	9/9	4/6
GCS *	14.8 \pm 0.5	12.9 \pm 2.0	10.0 \pm 1.8
Total infarct volume (mm ³)	31120.6 \pm 55826.9	34898.5 \pm 60729.2	28604.0 \pm 43300.4
CKMB (ng/ml)	3.6 \pm 1.1	7.3 \pm 10.2	3.9 \pm 2.9
NT-proBNP (pg/ml)**	522.9 \pm 957.0	2005.1 \pm 2268.2	1674.8 \pm 2659.9
Hospitalization (day)	9.3 \pm 3.6	12.9 \pm 8.2	12.1 \pm 6.9
Pulse (/min)	74.9 \pm 13.3	84.9 \pm 18.6	81.5 \pm 16.8
QT (ms)	390.0 \pm 27.4	395.6 \pm 53.4	374.0 \pm 35.3
cQT (ms)**	432.9 \pm 36.2	463.0 \pm 36.8	431.4 \pm 33.1
QTd (ms)	41.8 \pm 16.2	43.3 \pm 15.7	42.0 \pm 17.5
cQTd (ms)	47.1 \pm 20.7	51.0 \pm 16.7	49.8 \pm 25.0

* P<0.005, ** p<0.05,

SD: Standart deviation, GCS; Glasgow Coma Scale, NIHSS; National Institutes of Health Stroke Scale, CKMB; Creatine kinase MB, NT-proBNP; NT pro B-type natriuretic peptide, QT; QT duration, cQT; corrected QT duration, QTd; QT dispersion duration, cQTd; corrected QT dispersion duration.

When the patients were classified to have mild, moderate or severe stroke according to the NIHSS classification, the NT-proBNP values and cQT values increased significantly as the GCS value decreased (Table 2). However, there was no difference between age, sex, total infarction area, mortality and the QTd.

There was a negative correlation between the NIHSS and the GCS. The NT-proBNP had correlation with the NIHSS, GCS, cQT, QTd and cQTd (Figure 2a, 2b and 3). Multivariate linear regression analysis showed that the independent parameters that had an effect on the corrected NT-proBNP were the GCS and the cQT interval values (Table 3).

DISCUSSION

In this study, we found that the NT-proBNP levels in the ischemic stroke patients with no known cardiac pathology were markedly increased and this increase was associated with GCS, NIHSS, cQT, QTd. In addition, GCS and the cQT interval values were independent parameters associated

with raised NT-proBNP.

ECG changes such as the repolarization abnormalities, ST segment and T wave alterations, prolongation of the QT interval and the presence of abnormal Q waves have been known to take place in acute cerebrovascular events. However a study that compared the ECGs of the normal population with the ECGs of the patients with ischemic stroke has shown similar ECG changes in both groups, and these changes were highly correlated with age.² In this study ischemia like alterations (Left bundle branch block, severe or moderate T wave negativity, ST depression, Q wave and QS formation) in the ECGs of the healthy individual between the ages 65-74 years were found to be 31% among the females and 27% among the males, and in patients with ischemic stroke with no known cardiac problems changes in the ECGs were found to be 32%. In two other studies in stroke patients, Oppenheimer *et al.* and Buzluolcay *et al.* reported the rate of ECG changes to be 15-30% and 41.3% respectively.^{10,11} In our study, 28% of the stroke patients had abnormal ECG.

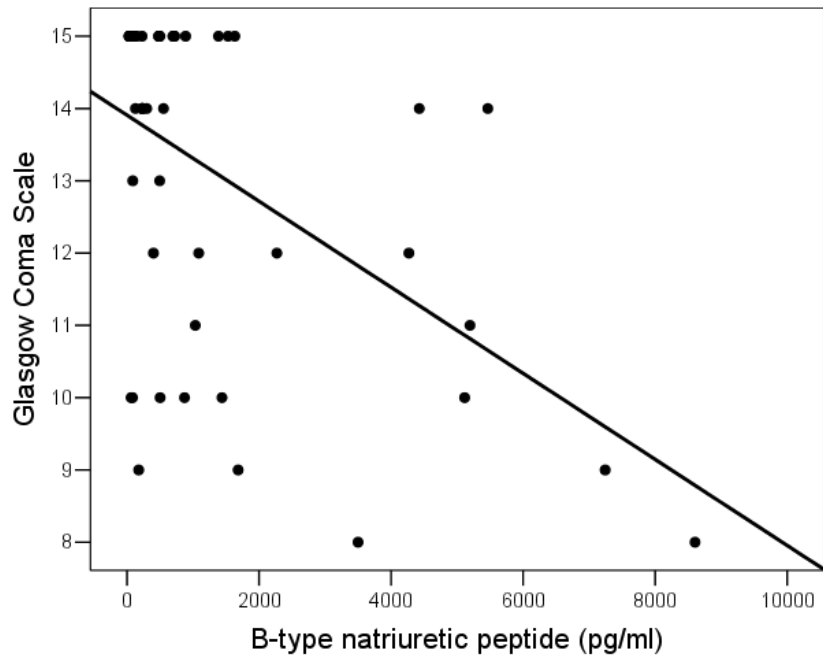


Figure 2a. Correlation of NT-proBNP and GCS

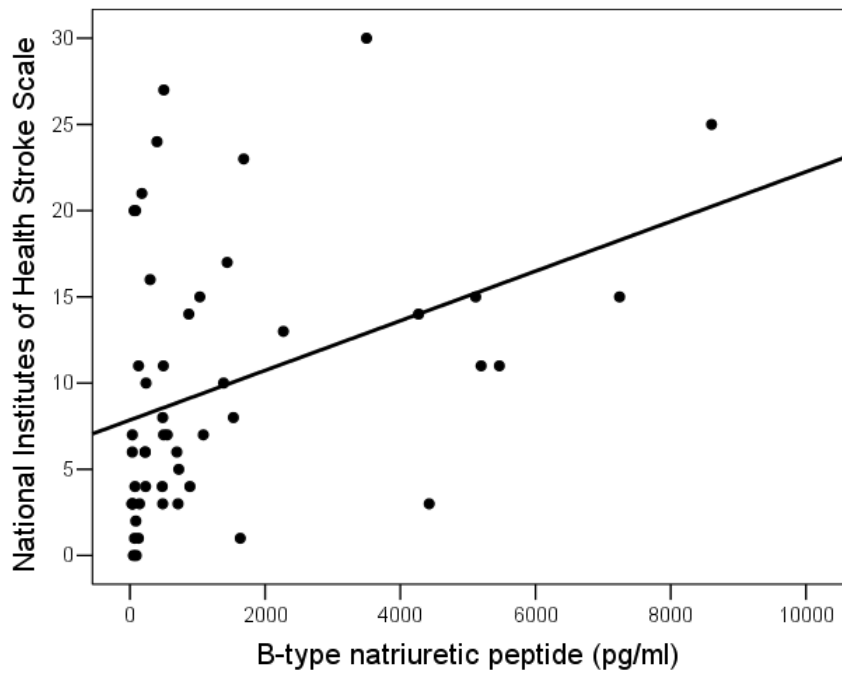


Figure 2b. Correlation of NT-proBNP and NIHSS

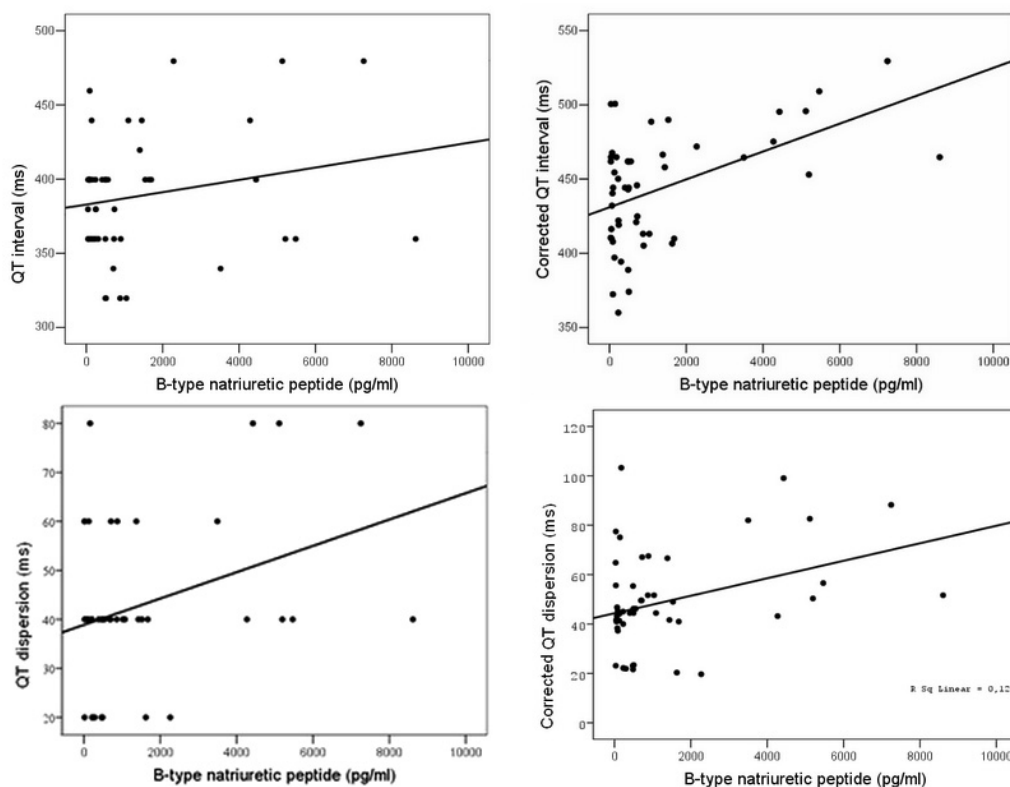


Figure 3. Correlation of NT-proBNP and QT, cQT, QTd, cQTd interval

Table 3: The independent parameters of NT-proBNP by univariate and multivariate linear regression analysis.

	Univariate analysis		Multivariate analysis	
	Pearson correlation coefficient	P value	Standardized β regression coefficients	P value
GCS	-0.514	<0.001	-0.466	<0.001
NIHSS	0.373	0.008	-0.168	0.440
Volume	-0.115	0.425	-0.118	0.277
QT	0.208	0.146	0.001	0.998
cQT	0.494	<0.001	0.444	<0.001
QTd	0.338	0.016	0.050	0.683
cQTd	0.355	0.011	0.033	0.796

GCS; Glasgow Coma Scale, cQT; corrected QT duration, NIHSS; National Institutes of Health Stroke Scale, QT; QT duration, QTd; QT dispersion duration, cQTd; corrected QT dispersion duration.

It has been showed that the pathologic ECG changes that are encountered in acute ischemic stroke patients are related with the involvement of the medulla oblongata, present hemodynamic disturbances and involved the sympathetic and the parasympathetic systems.¹⁰⁻¹⁶ An autopsy study of 8 stroke patients revealed diffuse myocardial necrosis, myocytolysis and hemorrhagic lesions in the areas of neural terminals in the myocardium and these were thought to be probably neurologic in origin.¹⁷

In this study, we have concentrated on the QT changes in ECG. When the patients were classified from mild, moderate to severe according to the NIHSS, we observed a significant increase in the NT-proBNP levels and cQTd from mild stroke towards moderate stroke. However age, sex and QTd remained unchanged. Moreover, total infarction volumes that were calculated by cerebral CT did not show a correlation with the QT changes and mortality.

QT prolongation is frequently encountered in ischemic stroke patients and it is a risk factor in the stroke outcome. The literature describes QT prolongation in approximately 25% of the stroke patients. In our patients, the cQT intervals of 29 (58%) patients were over 440ms and cQTd of 17 (34%) patients were above 50ms. ST segment changes and QT interval prolongation have been shown to increase the risk of death.^{2-4,16,18} Villa *et al.*¹⁶ have demonstrated the effect of QT prolongation on early mortality in acute ischemic stroke. Similarly Dogan *et al.*⁵ have shown the importance of ECG changes that included ischemia like alterations, prolonged QT interval and arrhythmias, on mortality within one month. In their study in 2006, FAMILONI *et al.*¹⁸ have also shown the association between the QT prolongation and mortality. On the other hand, although our study was not designed to determine mortality, we did not find an association between the cQT interval and mortality.

Another parameter that has an effect on mortality in acute ischemic stroke is the high NT-proBNP levels. Basically NT-proBNP is synthesized from the atrium and the ventricular myocardium. Its levels are elevated in patients with cardiac failure and in acute myocardial infarction and it is known to have a prognostic value.^{7,19,20} However NT-proBNP is also secreted from the ischemic brain tissue and its levels are increased during acute stroke.²¹⁻²⁴ Patients with acute myocardial infarction have been compared with patients having acute stroke and the NT-proBNP levels of the stroke patients have been found to

be higher.⁷ Our results are in conjunction with the literature in terms of NT-proBNP levels that were found to be high in acute ischemic stroke patients with no known cardiac pathologies. Furthermore we also found that the NT-proBNP levels of these patients had a positive correlation with the NIHSS values, a negative correlation with the GCS values, and also a positive correlation with the QT changes in ECGs. The independent risk factors affected by the NT-proBNP levels of these patients were found to be the GCS and cQT intervals by using the multivariate linear regression analysis. This finding shows that NT-proBNP, GCS and cQT are significantly associated in patients with cerebral stroke.

The relation between the increase of the extracardiac NT-proBNP levels and QT interval prolongation is not well known. In a study performed with the cirrhotic patients in whom extracardiac NT-proBNP levels were increased, a positive association between the increased NT-proBNP levels and prolonged QT intervals has been shown.²⁵ Our study also demonstrated that the elevated NT-proBNP levels had a correlation both with the cQT interval, the QTd and the cQTd.

In this study, we have concentrated on the QT changes. We did not observe the association between the QT interval prolongation and the mortality as described in the literature. We found that the NT-proBNP levels in the ischemic stroke patients were markedly increased and this increase was found to be correlated with the GCS and the corrected QT interval prolongation. Keeping this finding in mind, it is our opinion that the increased release of the NT-proBNP from the brain tissue is associated with the increased QT interval and QT dispersion in the ischemic stroke patients with no known cardiac pathology. More studies should be conducted to clarify this relationship.

The main limitation of this study was that the history obtained from the relatives of the patients was not very reliable. In particular, we were not able to determine the exact onset of the stroke before their arrival to our hospital, which may have affected the analysis. Also, greater sample size may help to reduce the high standard deviation values.

In conclusion, we have shown that, the NT-proBNP levels in the ischemic stroke patients with no known cardiac pathology were markedly increased. This increase was associated with the GCS, NIHSS, cQT, QTd and the cQTd interval. In addition the GCS and the cQT interval were independent parameters of the raised NT-proBNP.

DISCLOSURE

Conflict of interest: None

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