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Is Troponin really a reliable marker in patients with acute ischemic stroke?

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Background and purpose. Cardiac troponin I (cTnI) is a reliable marker to diagnose acute myocardial infarction, but the pathophysiological explanation for the increase in cTnI levels in patients with acute ischemic stroke (IS) remains unknown. To overcome this question, we aimed to compare serum cTnI levels in acute coronary syndrome (ACS) concomitant with and without stroke. By doing like this, we thought that we could demonstrate the effect of stroke on TrpI level.

Methods. Serum cTnI levels of 41 patients having ACS with acute IS during hospitalization were compared with 97 control patients having only ACS. Cranial CT was performed to evaluate the lesions. The severity of IS was evaluated objectively by national institutes of health stroke scale.

Results. cTnI levels were found to be similar in both groups. Presence of diabetes mellitus, coronary artery disease and previous myocardial infarction were more frequent in patients with acute IS. The cTnI levels in the patients with the cranial lesion in the anterior circulation was higher ($p = 0.039$). Presence of acute IS, cTnI level higher than 20 ng/mL and left ventricular ejection fraction < 40% were found to be independent risk factors for mortality ($p < 0.05$).

Conclusions. We found that abnormal troponin levels were more likely to be due to cardiac causes than cerebral ones in this first study evaluating the cTnI levels in patients with ACS concomitant with acute IS. The severity of IS, lesion location in the anterior circulation and higher troponin levels were associated with mortality.

Keywords: stroke, troponin I, acute coronary syndrome, brain ischemia, mortality.

INTRODUCTION

Cerebrovascular ischemic disease or ischemic stroke (IS) is one of the leading causes of mortality and morbidity in the general population [1, 2]. Myocardial ischemia (MI), Q-T prolongation and supraventricular/ventricular arrhythmias can accompany in the acute stage of IS [3]. Cardiac troponin is the most specific and sensitive laboratory marker to indicate myocardial damage .The serum level of cardiac troponin I (cTnI) which increases in the first 4 hours after the beginning of cardiac symptoms, peaks at 24 hours and remains high for up to 2 weeks because of the proteolysis of contractile components which is the most specific and sensitive laboratory marker to indicate myocardial damage [4]. Therefore, cTnI is accepted as a reliable marker to diagnose acute coronary syndrome (ACS) [4]. Increased cTnI levels can accompany other pathologies including IS, heart failure, septicemia, renal failure, pulmonary embolism and myocarditis, too [4, 5]. There are several studies in the literature showing that an increased cTnI level in acute IS has an impact on the prognosis [6-13]. The pathophysiological explanation for the increase in cTnI levels in patients with IS remains to be unknown. Serum cTnI level is a valuable indicator of cardiac ischemia and it can also increase during the acute stage of IS [3-5]. However, it is a diagnostic difficulty whether increased serum level of cTnI subsequent to myocardial damage is related to IS or ACS [6]. On the other hand, neurological myocardial damage is reversible which makes the differential diagnosis important [14]. To overcome these shortcomings, we evaluated the impact of cTnI increase to the clinical severity and mortality in patients who are admitted to hospital with the diagnosis of ACS and subsequent diagnosis of IS during the hospitalization period.

MATERIAL AND METHODS

Study population

In this study, we prospectively evaluated the patients who were hospitalized between November 2011 and January 2014 with the initial diagnosis of ACS and subsequent diagnosis of IS within the first 12 hours of hospitalization. Patients with other

DOI: 10.2478/rjim-2018-0016

diagnoses which could cause cTnI increase including congestive heart failure, acute pulmonary embolism, severe aortic stenosis, chronic kidney disease, pulmonary edema and malignity were excluded from the study. Baseline patient's characteristics including socio-demographic details and risk factors were recorded.

cTnI measurement and cardiac evaluation

cTnI levels were evaluated during the first 48 hours (3 or more measurements during 48 hours after ACS event; at the first presentation, 4th hour and then 3rd one at the 24th hour) in the hospital laboratory (Machine: Abbott diagnostic, Germany). The level of 0.06 ng/mL was accepted as the cut-off value. The highest cTnI level measured during the first 48 hours was accepted for comparison. The serum cTnI levels of the patients with ACS and acute IS were compared with the serum cTnI levels of sex and age matched patients with only ACS. Then, the participants were divided into three groups according to their cTnI levels (≤5 ng/mL, 5.1-19.9 ng/mL, ≥ 20 ng/mL) for another comparison. Transthoracic echocardiography (TTE) was performed during hospitalization and all patients were divided into two groups with respect to their left ventricular ejection fraction (LVEF) (< 40% and ≥ 40%).

Evaluation of stroke event

Patients who had a stroke underwent cranial CT exam (64-slice machine: Siemens, Erlangen, Germany) firstly at admission and secondly after 48 hours and lesion localizations were recorded. Cranial MRI was performed in case of indefinite diagnosis with negative CT patients because ischemic lesions cannot be seen in early hours. Cranial lesions were evaluated according to their localization as anterior and posterior circulation.

Clinical severity of stroke was determined by using national institutes of health stroke scale (NIHSS) and outcome was measured by modified Rankin scale (mRS). Acute stroke patients were divided into three groups according to the NIHSS score at the arrival time to the hospital as mild < 8, moderate (between 8 and 16), severe >16. In addition, they were divided into two groups according to the mRS value before patients are discharged as clinically independent (SCORE ≤ 2) and clinically dependent (SCORE ≥ 3) in daily activities [15]. The study was in compliance with the principles outlined in the Declaration of Helsinki and approved by the Institutional Ethic Committee.

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) softwares were used. Mean and standard deviations were used for quantitative variables. Student T test was used for normally distributed variables in both groups and Mann Whitney U test was used for variables which were not normally distributed. Q variables were evaluated by Pearson Chi-square test, Yates continuity test, Fisher's Exact Test and Fisher-Freeman-Halton Test (Monte Carlo). Logistic regression model was used on multivariate analysis to identify risk factors related to mortality. A p value of < 0.05 was accepted statistically significant.

RESULTS

The patients and controls were selected by a randomized method from the patients admitted to Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Research Center with the initial diagnosis of ACS between 1 November 2011 and 31 January 2014. In the present study, we enrolled 86 ACS patients as the study group who were subsequently diagnosed as acute IS during their hospitalization and 97 patients with the diagnosis of ACS as control group. In the study group, patients with diagnoses which can cause cTnI level elevation such as congestive heart failure, chronic renal disease, acute pulmonary edema and malignity were excluded (n:14). Also, patients who underwent urgent revascularization at the time of presentation to the hospital were excluded from the study group (n: 31). The remaining 41 patients were accepted for the study and all of them had percutaneous coronary intervention (PCI). There was not any IS related to PCI.

The mean ages of study and control groups were 67.59 ± 11.18 and 66.57 ± 12.88 (years, p = 0.660) respectively. Table 1 shows the other socio-demographic and clinical data of both groups. As it was seen there, 97 patients were diagnosed as only ACS while 41 of the patients had concomitant IS. There were no statistically significant differences in mean age, gender and level of troponin between study and control groups (p > 0.05). Presence of diabetes mellitus, coronary artery disease and previous myocardial infarction were more frequent in patients with acute IS (Table 1). Diabetes mellitus (OR: 6.013 with CI 95% 2.67-13.50), previous coronary artery disease (OR: 5.636 with CI 95% 1.59-19.95) and previous myocardial infarction (OR: 3.000 with CI 95% 1.24-7.23) were associated with increased

risk for acute IS. NIHSS score mean was 15.39 ± 8.64 (Range: 4-30) and according to mRS scores 9 patients (22%) were independent in daily activities and 32 patients (78%) were dependent in daily activities. The clinical and laboratory variables in patients with acute IS were shown in Table 2. In addition, no statistically significant difference was found between cTnI level and dependency to other degrees as evaluated by mRS scale (a Fisher Freeman Halton – Monte Carlo, $p > 0.05$). The average values of cTnI levels in patients with the cranial lesion in the anterior circulation and posterior circulation were 26.63 ± 19.05 ng/mL (Range: 0.11 ng/mL to 50 ng/mL, Median = 20) and 11.19 ± 12.50 (Range: 0.80 ng/mL to 42 ng/mL, Median = 12) respectively (MWU, $p = 0.039$). For a group of patients with cTnI levels; ≤ 5ng/mL, 5.1-19.9 ng/mL and ≥ 20 ng/mL cranial lesions were located in the anterior circulation 54.5%, 63.6%, 89.5% respectively and in the posterior circulation 45.5%, 36.4%, 10.5% respectively.

Table 1
Analysis of defining characteristics of groups

		Study Group n = 41(%)	Control Group n = 97 (%)	p
Gender	**Female**	20 (48.8)	53 (54.6)	[b]*0.529*
	Male	21 (51.2)	44 (45.4)	
In-hospital mortality		13 (31,7)	9 (9.3)	[c]***0.002***
HT		38(92.7)	81 (83.5)	[b]*0.246*
DM		23 (56.1)	17 (17.5)	[b]***0.001***
HL		7 (17.1)	22 (22.7)	[c]*0.610*
AF		9 (22)	11 (11.3)	[c]*0.176*
CAD		8 (19.5)	4 (4.1)	[d]***0.006***
Previous STROKE		3 (7.3)	5 (5.2)	[d]*0.695*
Previous MI		13 (31.7)	13 (13.4)	[b]***0.012****
EF (%) (<40)		12 (29.3)	27 (27.8)	[b]*0.864*
Troponin I (ng/mL)	**< 5**	11 (26.8)	28 (28.9)	[b]*0.922*
	5.1-19.9	11 (28.8)	23 (23.7)	
	> 20	19 (46.3)	46 (47.4)	

[a]Student-t test, [b]Pearson chi-square test, [c]Yates Continuity Correction test, [d]Fisher's exact test (*p < 0.05,**p < 0.01)
HT: Hypertension, DM: diabetes mellitus, HL: hyperlipidemia, AF: atrial fibrillation, CAD: coronary artery disease, MI: myocardial infarction, EF: ejection fraction

Table 2
Distribution of variables in patients with acute stroke

		Number of patients (n:41)	Mean ± SD	Min-Max values
Troponin I			21.75 ± 18.55	0.11–50
NIHSS score			15.39 ± 8.64	4–30
Troponin I	**< 5**	11 (26.8%)		
	5.1-19-9	11 (26.8%)		
	> 20	19 (46.3%)		
mRS score	**Independent in daily activities**	9 (22%)		
	Dependent in daily activities	32 (78%)		
Lesion localization	**Anterior**	30 (73.2%)		
	Posterior	11 (26.8%)		
Lesion size	**> 3cm**	27 (65.9%)		
	< 3 cm	14 (34.1%)		
HR			88.00 ± 14.56	61–132
PR Interval			165.68 ± 27.36	116–244
QRS Duration			97.10 ± 16.24	72–146
QT			392.60 ± 44.46	304–552
QTC Interval			425.58 ± 30.94	372–532
RBBB		1		
LBBB		3		
Q Wave		22		
ST-segment Elevation		12		
ST-segment Depression		17		
LVH		9		
T Wave inversion		11		
Pacemaker		1		

NIHSS: national institutes of health stroke scale, mRS: modified rankin scale, HR:heart rate, RBBB: right bundle branch block, LBBB: left bundle branch block, LVH: left ventricular hypertrophy

Table 3
Analysis on in-hospital mortality

Study group		In-hospital mortality *The number of patients & percentages n (%)*		p value
		No (n = 28)	**Yes (n = 13)**	
Age (year)	**Mean±SD**	66.61 ± 10.84	69.69 ± 12.04	***0.623***
	Min-Max (median)	43-85 (67)	55-92 (69)	
Lesion size *n (%)*	**> 3**	16 (57.1)	11 (84.6)	***[b]0.156***
	< 3	12 (42.9)	2 (15.4)	
mRS score; *n (%)*	**independent in daily activities**	8 (28.6)	1 (7.7)	***[b]0.228***
	dependent in daily activities	20 (71.4)	12 (92.3)	
Lesion localization *n (%)*	**Anterior**	17 (60.7)	13 (100.0)	***[b]0.008*****
	Posterior	11 (39.3)	0 (0.0)	
NIHSS score *n (%)*	**Mild**	9 (32.1)	1 (7.7)	***[a]0.000*****
	Moderate	12 (42.9)	0 (0.0)	
	Severe	7 (25.0)	12 (92.3)	
EF *n (%)*	**< 40**	6 (21.4)	6 (46.2)	***[b]0.146***
	≥ 40	22 (78.6)	7 (53.8)	
Troponin I	**Mean ± SD**	17.94±17.02	29.94 ± 19.71	***[c]0.049****
	Min-Max (median)	0.11-50 (12)	0.70-50 (26)	
Troponin I Level *n (%)*	**≤ 5**	9 (32.1)	2 (15.4)	
	5.1 – 19.9	8 (28.6)	3 (23.1)	
	≥ 20	11 (39.3)	8 (61.5)	

[a]FisherFreemanHalton Test (Monte Carlo). [b]Fisher's Exact Test. [c]MannWhitney U test. **p < 0.01
NIHSS: national institutes of Health Stroke Scale, mRS: modified rankin scale, EF: ejection fraction

The hospital mortality rates were statistically higher in patients with acute IS (31.7%) as compared to control group (9.3%) (p < 0.01, OR: 4.540, CI 95%: 1.76-11.74). Acute IS increased the mortality rate up to 4.5 fold in patients with ACS. The model created and evaluated by using logistic regression analysis with respect to impact of diabetes mellitus, coronary artery disease, atrial fibrillation, previous myocardial infarction, ejection fraction rate, grouped cTnI levels and presence of acute IS to the mortality was found to be statistically significant with the regression ratio (84.2%). The presence of acute IS [OR:5.066 (95% CI:1.84-13.15)], cTnI level higher than 20 ng/mL [OR:3.936 (%95 CI:1.01-15.33), p = 0.048] and EF less than 40% [OR: 4.463 (%95 CI: 1.63-12.24), p = 0.004] were found to be independent risk factors for mortality. As seen in Table 3, lesion location in the anterior circulation increased NIHSS score and elevated cTnI levels were associated with higher mortality rates in patients with acute IS (p = 0.008, p = 0.000, p = 0.049 respectively).

DISCUSSION

The measurement of cTnI is recommended for early management of patients with acute ischemic stroke by the guidelines but pathophysiological mechanism of cTnI elevation in stroke patients still remains unknown [16]. Although the most common ECG findings in stroke patients are patterns of ischemic changes and it may explain the cTnI increase as a consequence of myocardial damage, it is not easy to identify the etiology of cTnI increase which can be the consequence of cerebral or myocardial damage or comorbid diseases in patients with acute IS [17]. The relative changes in epinephrine and cortisol levels, the imbalance between the parasympathetic and sympathetic nervous systems and myocardial damage are considered to be possible mechanisms for cTnI levels [8, 18, 19]. Kerr G. *et al*. reported cTnI increase in 18% of acute stroke patients and the ratio of patients with high level of cTnI in these studies were varied (0-35%) which was attributed to patient exclusion criteria, cut-off differences between studies and whether the exclusion of patients with other diseases that can cause cTnI level increase in a meta-analysis [6]. Some newly pressed studies showed that elevation of cTnI could be seen in ischemic stroke and lots of them had CAS as well [20-22]. In our study, the ratio of patients with IS among ACS patients was found to be 2.71% (n: 86) which was consistent with the ratios found in previous studies [23, 24]. In the present study, most of the patients with acute IS concomitant with ACS and the patients with ACS have increased level of cTnI but cTnI levels were found to be similar in both groups. This finding was an important data regarding the question that was not answered for years.

In previous neuro-imaging studies evaluating the impact of cTnI increase to clinical severity and mortality, it was found that cTnI levels were higher in patients with acute stroke whose lesions were located in the anterior circulation [13, 25-28]. The results of our study were consistent with previous studies and cTnI levels were higher in stroke patients whose lesions were located in anterior circulation. Another important finding was that 17 patients with cTnI level ≥ 20 ng/mL (89%) had a lesion located in the anterior circulation. ECG examination in acute stroke patients with elevated cTnI level is important to evaluate myocardial ischemia patterns [29, 30]. Fure B. *et al*. reported a relationship between ST segment-depression and Q wave on ECG with troponin-T level which was associated with worse clinical prognosis in short-term follow-up [3]. Q wave on ECG examination was the most frequent finding (n: 22, 55%) in our study as shown in Table 2. However, to attribute this finding to acute stroke is not accurate due to presence of myocardial ischemia in our study population.

There are several studies emphasizing the relationship between cTnI levels with prognosis and mortality in the literature [8, 11, 13, 30, 31]. Despite the findings from the previous studies which reported a positive correlation between cTnI levels with clinical stroke severity, we found no relationship between these two variables in our study [8, 9, 13, 27, 28, 30-32]. Additionally, the relationships between grouped-cTnI levels and clinical severity (NIHSS) and between cTnI levels and dependency scale scores (mRS) were similar, too. Therefore, we believe that there is a strong possibility that the elevated cTnI levels in acute IS patients are associated simply with concomitant ACS. On the other hand, mortality studies found that elevated cTnI levels are associated with increased mortality in patients with acute IS [10, 11, 32, 33]. Faiz *et al*. evaluated serial cTnI levels in 264 acute stroke patients after excluding the patients with ACS and reported that there was a strong correlation between cTnI levels and in-hospital mortality. They emphasized the importance of the rate of increase in cTnI level rather than the baseline value in acute stroke patients. They also reported the possibility of short term elevation in cTnI levels caused by the presence of previous chronic diseases [34]. In a similar study, researchers demonstrated highly increased level of cTnI in 5.5% of total 330 acute IS patients. In-hospital and 6 month follow-up mortality rates were found to be significantly higher in the group of patients with elevated cTnI [9]. In our study, acute IS patients with higher cTnI level (≥ 20 ng/mL) had statistically significant increased rate of mortality compared to patients with lower cTnI level (< 20ng/mL) ($p = 0.049$). In logistic regression analysis cTnI level ≥ 20 ng/mL was found to be an independent risk factor on in-hospital mortality rate [ODDS 3.936 (%95 CI: 1.01-15.33), $p = 0.048$]. Of course, the positive correlation between cardiac pathologies and cTnI levels is well known. Because of low significancy, analyzing the rate of increase in cTnI level and concomitant cardiac damage seems to be more accurate instead of evaluating the rate of mortality by taking one basal cTnI value into account in acute IS patients. Apart from these, another important finding from our study was the increased rate of in-hospital mortality in ACS patients with acute IS compared to the ACS patients without acute IS (31.7% *vs*. 9.3% respectively as seen Table 1). In our study, the presence of diabetes mellitus, coronary artery disease and previous myocardial infarction were more frequent in patients with acute IS (Table 1). DM increased the risk of acute IS 6-fold, coronary artery disease and previous MI increased the risk of acute IS 5.6 and 3-fold respectively. Complications of DM, recurrent coronary artery disease and myocardial infarction were considered to be risk factors for acute IS patients associated with increased disability and mortality. This was an important finding addressing that we should be more careful about the patients with previous histories of diabetes mellitus or cardiac problems. We believe that our findings are valuable because possible pathophysiological mechanisms of cTnI increase in acute stroke patients were not addressed particularly in previous studies. To use as a predictor for acute stroke, exclusion of other diseases which can cause elevation in cTnI levels and demonstrating the progressive increase from the baseline cTnI values are necessary. We excluded all other diseases elevating cTnI values and evaluated cTnI values of ACS patients with IS and cTnI values of ACS patients without IS. Both study and control group patients enrolled in the present study were diagnosed as ACS which was convenient to evaluate the reason for cTnI level increase in acute stroke patients. They were compared and it was logical because the measurement of cTnI was accepted as diagnostic criterion for ACS [35, 36].

In conclusion, cTnI levels were not considered to be a reliable acute phase reactant in acute IS patients. To best of our knowledge, this is the first study evaluating the cTnI levels in patients with ACS concomitant with acute IS and without acute IS. As it was mentioned above, cTnI levels were

found to be similar in both groups and it was an important data regarding the question that was not answered for years. By analyzing the patients with acute IS, it revealed that cerebral lesion localization in the anterior circulation, cTnI levels ≥ 20 ng/mL and LVEF < %40 were associated with increased rate of morality. Despite all of these findings, absence of statistical significant correlation between cTnI levels with clinical stroke severity (according to NIHSS or mRS scores) lead to the possibility that higher mortality rates in acute stroke patients with increased cTnI levels is attributed to cerebral causes rather than cardiac origin. Therefore, further cardiac evaluation has paramount importance for acute stroke patients whose cTnI levels are elevated.

Conflict of interest. The authors have no conflict of interest to declare.

Acknowledgment. Some parts of the data in the manuscript were presented at the 10th World Stroke Congress in Hyderabad, India, from 26-29 October, 2016.

Introducere. *Troponina I cardiacă (cTnI) este un biomarker pentru diagnosticul infarctului miocardic însă explicațiile fiziopatologice ale creşterii cTnI la pacienții cu atac vascular cerebral ischemic (IS) rămân necunoscute. Scopul studiului a fost de a compara nivelurile serice ale cTnI la pacienții cu sindorm coronarian acut (ACS) care au avut sau nu IS în acelaşi timp.*

Materiale si metode. *Nivelurile serice ale cTnI de la 41 de pacienți cu ACS şi IS acut în timpul spitalizării au fost comparate cu nivelurile înregistrate la 97 de pacienți care aveau numai ACS. Evaluarea leziunilor cerebrale a fost realizată cu ajutorul CT cranian. Severitatea IS a fost evaluată obiectiv folosind scala National Institute of Health Stroke.*

Rezultate. *Nivelurile cTnI au fost similare în ambele grupuri. Prezența diabetului, a bolii coronariene şi a infarctului miocardic în antecedente au fost mai frecvente la pacienții cu IS acut. Nivelurile cTnI au fost semnificativ statistic mai mari la pacienții cu leziuni ischemice în cadrul circulației anterioare cerebrale ($p = 0.039$). Prezența IS acut, a concentrațiilor cTnI mai mari de 20 ng/mL şi a fracției de ejecție ventriculare stângi <40% au fost factori independenți de risc pentru mortalitate ($p < 0.05$).*

Concluzii. *Nivelurile anormale ale cTnI la pacienții care au ACS concomitent cu IS par să aibă origine cardiacă, acesta fiind primul studiu care a evaluat nivelurile cTnI la pacienții cu ACS şi IS concomitent. Severitatea IS şi localizarea leziunii în teritoriul cerebral anterior împreună cu niveluri mai mari ale troponinelor s-au asociat cu mortalitatea.*

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Received March 5, 2018