

Clinical Article

Initial Troponin Level as a Predictor of Prognosis in Patients with Intracerebral Hemorrhage

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Objective : It has been suggested that elevated cardiac troponin T (cTnT) level is a marker of increased risk of mortality in acute ischemic stroke and subarachnoid hemorrhage (SAH). However, the association of serum cTnT level and prognosis of intracerebral hemorrhage (ICH) has been sparsely investigated. The aim of this study was to identify the relationship between cTnT level and the outcome in patients with spontaneous ICH.

Methods : We retrospectively investigated 253 patients identified by a database search from records of patients admitted in our department for ICH between January 1, 2003 and December 31, 2007. The patients were divided into 2 groups; the patients in group 1 (n=225) with serum cTnT values of 0.01 ng/mL or less, and those in group 2 (n=28) with serum cTnT values greater than 0.01 ng/mL.

Results : The serum cTnT level was elevated in 28 patients. There were significant differences in sex, hypertension, creatine kinase-myocardial band, midline shift, side of hematoma, and presence of intraventricular hemorrhage between the 2 groups. Logistic regression analysis identified the level of consciousness on admission, cTnT and midline shift as independent predictors of hospital mortality.

Conclusion : These results suggest that increased serum cTnT level at admission is associated with in-hospital mortality and the addition of a serum cTnT assay to routine admission testing should be considered in patients with ICH.

KEY WORDS : Cardiac troponin T · Intracerebral hemorrhage · Outcome.

INTRODUCTION

Intracerebral hemorrhage (ICH) is associated with considerable morbidity and mortality, with estimates of 30-day mortality ranging from 10 to 52%^{2,24}. It accounts for approximately 10-20% of all strokes⁶.

Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are currently the tests of choice for the detection of myocardial injury¹. Elevated cTnT level and cardiac injury in patients with subarachnoid hemorrhage (SAH) has been well recognized^{8,16,28,30,31} and more recently they have been associated with a stunned myocardium, resulting in pump failure and congestive heart failure²¹. The presence of elevated values of cardiac troponin in patients with acute neurologic diseases has been associated with an adverse prognosis. In a study of a heterogeneous group of patients with stro-

kes, head injuries, and seizures, elevated cTnI levels were observed in 19% of the patients and correlated with poor prognosis¹⁰. It has been suggested that elevated troponin may be a marker of increased mortality in patients with acute ischemic stroke^{9,17}, although some investigators reported no relationship between cTnT and prognosis^{4,12}. However, only a few studies have examined the relation between cTnT and prognosis of ICH, and results were largely inconclusive^{15,22}.

In this study, we sought to identify the relationship between cTnT and outcome in patients with spontaneous ICH.

MATERIALS AND METHODS

Patient identification and exclusion

Patients were retrospectively identified by a search of neurosurgical records for ICH between January 1, 2003 and December 31, 2007. The inclusion criteria for the study were as following : 1) spontaneous ICH, 2) measurement of serum cTnT level and electrocardiography were performed within 24 hours of insult, 3) patients older than 18 years old, and 4) availability of medical records includ-

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ing at least one Computed Tomography (CT) scan. The exclusion criteria were infratentorial ICH, drug abuse and ICH secondary to trauma, neoplasm, vascular malformation or aneurysm, hemorrhagic transformation of infarction, and use of thrombolytic agents. Other exclusion criteria were any ischemic heart disease, including previous myocardial infarction, symptoms suggestive of acute myocardial infarction or unstable angina before admission, as well as previous coronary angioplasty or bypass surgery.

Clinical data collection

Clinical data, including age, sex, significant comorbid conditions, creatine kinase myocardial band isoform (CK-MB) and admission Glasgow coma scale (GCS) score were obtained by chart review. Hypertension, diabetes mellitus, and smoking history were considered significant comorbid conditions. A standard 12-lead ECG was performed at admission, and additional ECGs were obtained if there were abnormalities in rhythm or morphology. Cardiologists interpreted all of the ECGs. Outcomes were assessed at the time of death or 1 month post-ICH using the five-point GOS.

ICH evaluation

Initial cranial CT scans were evaluated in order to determine the location and volume of the hemorrhage, midline shift, and the presence of intraventricular hemorrhage (IVH). Supratentorial ICH was classified as deep (originating in the thalamus, basal ganglia, or external capsules) or lobar. The volume of the hemorrhage was estimated using the formula $(ABC)/2$ where A, B, and C represent the respective diameters⁵. The midline shift was measured as the distance from either the septum pellucidum or pineal gland to the line connecting the anterior and posterior reflections of the falx cerebri.

Troponin assay

Initial cTnT within 24 admission hours was recorded for each patient. Serum cTnT was measured from venous blood samples using the Elecsys 2010 platform (Roche Diagnostics, Mannheim, Germany). A serum cTnT value ≥ 0.01 ng/mL was set as the cut-off value in our laboratory.

Statistical analysis

A spreadsheet with statistical functions (Microsoft Excel; Microsoft Corp., Redmond, WA) was used for all preliminary calculations. All other analyses were performed using a statistical software package (SPSS for Windows version 10.0 : SPSS INC., Chicago, IL). Comparisons of the categorical variables were made using the Chi-square

test or Fisher's exact test. Continuous variables were compared among groups using the Student's t-test. Logistic regression analyses were performed with adjustments for demographic, clinical and radiographic predictors of mortality in ICH to determine whether elevated cTnT is an independent predictor of mortality.

RESULTS

Patient characteristics

A total of 253 patients were enrolled in this study. The patients ranged in age from 23 to 88 years (mean age, 59.8 years), and 60.5% were male. The location of the supratentorial ICH was ganglionic in 159 patients, thalamic in 52, external capsular in 2, and lobar in 40. Right-sided supratentorial ICH occurred in 117 patients, intraventricular extension of ICH was found in 85 patients, and subarachnoid extension was observed in 18 patients. A cTnT assay was performed in all patients. The serum cTnT level was elevated in 28 patients.

Comparison between the 2 groups and predictors of hospital mortality

Serum cTnT levels on admission were elevated in 28 (11.1%) of the 253 patients. The patients were divided into 2 groups : the patients in group 1 had serum cTnT values of 0.01 ng/mL or less, and those in group 2 had cTnT values greater than 0.01 ng/mL. Although there was no significant difference in age, diabetes mellitus, smoking history, and level of consciousness between 2 groups, there were significant differences in sex, history of hypertension, CK-MB level. Their *p* values were 0.038, 0.024, and 0.036 respectively. Mortality was 7.6% in group 1 and 28.6% in group 2. Outcome differed considerably between 2 groups (Table 1). In radiologic features, there were significant differences in midline shift (*p*=0.041), side of hemorrhage (*p*=0.042), and presence of IVH (*p*=0.018). Amount of hematoma was 26.18 ± 28.96 mL in group 1 and 38.64 ± 38.42 mL in group 2. Location of hemorrhage, SAH extension, and amount did not differ between groups (Table 2).

Logistic regression analysis by use of enter method, identified level of consciousness on admission, midline shift and cardiac troponin level ≥ 0.01 ng/mL as independent predictors of hospital mortality. In final model, dependent variables included level of consciousness on admission, SAH, IVH, cTnT, hematoma amount and midline shift and other variables were excluded because *p*-value was not statistically significant (*p*-value>0.05). When the model was applied to the data set, 92.1% of the patients were correctly classified. The parameter estimates, standard errors, odds

Table 1. Demographic and clinical characteristics of patients

Characteristic	No. of patients (%)		p value
	Group 1 (cTnT≤0.01 ng/mL) (n=225)	Group 2 (cTnT>0.01 ng/mL) (n=28)	
Age(years)	59.33±12.88	63.54±10.78	0.099
Sex			0.038 [†]
Male	131 (58.2)	22 (78.6)	
Female	94 (41.8)	6 (21.4)	
Medical History			
Diabetes	56 (24.9)	9 (32.1)	0.407
Hypertension	118 (52.4)	21 (75.0)	0.024 [†]
Smoking	120 (53.3)	18 (64.3)	0.272
Level of consciousness at admission			0.353
GCS score 3-8	47 (20.9)	8 (28.6)	
GCS score 9-15	178 (79.1)	20 (71.4)	
CKMB	2.98±2.01 ng/mL	4.70±4.08 ng/mL	0.036 [†]
Outcome			
Dead	17 (7.6%)	8 (28.6%)	0.002 [†]

[†]Data are presented as n (%) or mean±standard deviations. [†]Statistically significant difference between groups ($p<0.05$). cTnT=cardiac troponin, T CK-MB : creatine kinase-myocardial band isoform, GCS : Glasgow Coma Scale

Table 2. Radiologic characteristics of patients

Characteristic	No. of patients (%)		p value
	Group 1 (cTnT≤0.01 ng/mL) (n=225)	Group 2 (cTnT>0.01 ng/mL) (n=28)	
Location			0.058
Deep	193 (85.8)	20 (71.4)	
Ganglionic	144 (74.6)	15 (75.0)	
Thalamic	47 (24.4)	5 (25.0)	
External capsule	2 (1.0)	0	
Lobar	32 (14.2)	8 (28.6)	
Frontal	5 (15.6)	2 (25.0)	
Temporal	11 (34.4)	0	
Parietal	8 (25.0)	1 (12.5)	
Occipital	2 (6.3)	2 (25.0)	
Extensive	6 (18.8)	3 (37.5)	
Side			0.042 [†]
Right	99 (44.0)	18 (64.3)	
Left	126 (56.0)	10 (35.7)	
Extension			
SAH extension of ICH	16 (7.1)	1 (3.6)	0.703
IVH extension of ICH	70 (31.1)	15 (53.6)	0.018 [†]
Amount of hematoma	26.18±28.96 mL	38.64±38.42 mL	0.107

[†]Data are presented as n (%) or mean±standard deviations. [†]Statistically significant difference between groups ($p<0.05$). cTnT : cardiac troponin T, ICH : intracerebral hemorrhage, IVH : intraventricular hemorrhage, SAH : subarachnoid hemorrhage

ratios, and p -values for variables are summarized in Table 3.

ECG changes

Changes in ECGs were seen in 108 patients. The common rhythm abnormalities were first-degree heart block, right bundle branch block, and premature ventricular com-

plex in group 1 and right bundle branch block and sinus tachycardia in group 2 (Table 4). There was no significant difference in ECG changes between 2 groups, but ischemic ECG change was suspected in 6 patients of group 2.

DISCUSSION

It is widely accepted that cTnT is a more specific marker for myocardial damage than CK-MB in patient with coronary artery disease. cTnT is one of the troponin group and a thin filament protein which takes part in muscle contraction. The troponin group consists of troponin C, troponin I and troponin T. The troponin complex on the actin filaments regulates the force and the velocity of muscle contraction. Troponin C functions as a calcium-receptor while troponin I prevents the adenosine triphosphatase activity when bound to actin. Troponin T fixes the troponin group to tropomyosin²⁹. After myocardial cell damage, troponins are released from the myocytes. The cTnT levels are detectable in 3-12 hours after the myocardial injury, and the concentration is in direct proportion to the extent of myocardial injury. Mean time to peak cTnT level is about 12-48 hours. The concentration returns to normal range after 5-14 days. The cTnT is very cardiac specific, and it is not present in the serum following nonmyocardial muscle or other tissue damage¹⁸.

Cardiac troponin elevations have been reported in numerous conditions such as sepsis, pulmonary embolism, pericarditis, chronic renal failure, major trauma, stroke and SAH^{3,14,19}. The

presumed cause for this elevation in acute neurologic disease is related to an increase in systemic catecholamines⁴. This association has not been fully described in ICH. This study shows that elevated cTnT level is associated with poor outcome in patients with spontaneous ICH.

The mechanism of cardiac dysfunction after aneurysmal

Table 3. Multivariate analysis of risk of in-hospital mortality

Parameter	Parameter estimate>B	p-value	Adjusted OR	95% of C.I. for Adjusted OR	
				Lower	Upper
Level of consciousness	2.357	0.001*	10.563	2.685	41.552
SAH	0.780	0.345	2.181	0.432	11.000
IVH	0.977	0.107	2.655	0.810	8.706
cTnT (group 1, 2)	1.526	0.044*	4.601	1.040	20.361
Amount of hematoma	-0.006	0.580	0.994	0.974	1.015
Midline shift	0.235	0.008*	1.264	1.063	1.504

*Statistically significant difference between groups (p<0.05). cTnT : cardiac troponin T, IVH : intraventricular hemorrhage, OR : Odds Ratio, SAH : subarachnoid hemorrhage.

Table 4. Types of ECG changes

ECG changes	No. of patients (%)	
	Group 1 (n=93) (cTnT≤0.01 ng/mL)	Group 2 (n=15) (cTnT>0.01 ng/mL)
Sinus bradycardia	7 (3.1)	1 (3.6)
Sinus tachycardia	7 (3.1)	2 (7.1)
Premature ventricular complexes	9 (4.0)	0
Atrial fibrillation or flutter	4 (1.8)	1 (3.6)
Right bundle branch block	11 (4.9)	3 (10.7)
ST-T morphologic changes	22 (9.8)	1 (3.6)
First-degree heart block	11 (4.9)	1 (3.6)
Corrected QT interval prolongation	4 (1.8)	0
R/O ischemia	18 (8.0)	6 (21.4)

cTnT : cardiac troponin T

SAH is not fully understood. Autopsy studies have reported that SAH results in vascular damage to hypothalamus¹¹. Most studies implicate the hypothalamus as the primary center of dysfunction^{13,23}. Stimulating the posterior hypothalamus and midbrain reticular formation result in ECG changes similar to those following SAH²⁵. The assertion that cardiac alterations are mediated by catecholamine is supported by the fact that disrupting the sympathetic chain at the cervical level stops the arrhythmias, whereas a vagotomy does not^{20,30}. These changes can be inhibited by catecholamine blocking agents⁷.

Another hypothesis suggests that after ischemic stroke, increased intracranial pressure or insular disinhibition leads to marked release of catecholamine by activation of central autonomic network, which can induce tachycardia, coronary vasospasm, coronary and peripheral vasoconstriction, and direct myocardial toxicity due to increased intracellular calcium²². The insula is the site for the integration of sensory, autonomic, limbic functions through its reciprocal connections with principal sensory areas, paralimbic areas in the orbital, temporopolar, and cingulate cortices, and hypothalamus²⁶. Right hemispheric strokes are more arrhythmogenic than left-sided strokes, involvement of the insular cortex predisposes patients to sudden cardiac death^{1,27,32}.

There are a few reports about relationship between elevated cTnT level and outcome in patients with ICH. Hays et

al.¹⁵ has reported that elevated cTnI values occur frequently in ICH and are independently associated with higher in-hospital mortality but Maramattom et al.²² has demonstrated contrary result that elevation of cTnT levels do not influence the early outcome of patients with ICH. In this study we report on the relationship between cTnT and outcomes in patients with ICH. An elevated cTnT group was associated with a higher mortality compared with a normal cTnT group (28.6% vs. 7.6%, p=0.002). Level of consciousness on admission, cTnT, and midline shift were independently associated with ICH mortality in this study.

There are several limitations to our study. The most important limitations are its retrospective nature and small sample size. A future prospective trial would be useful in order to definitively ascertain whether cardiac injury plays a role in morbidity and mortality resulting from ICH. Second, this study may have included patients with occult coronary artery disease who would be more likely to have cTnT elevations during the acute phase, which would have assisted in establishing the relationship to mortality. Third, because we could not test consecutive serum cTnT levels in all patients, our study relied on single baseline serum level. A consecutive assay could have provided additional information on the development and evolution of myocardial damage in patients with ICH.

CONCLUSION

This study shows that elevated cTnT levels in patients with ICH are related to poor outcomes. We suggest that the addition of a serum cTnT assay to routine admission testing should be considered in patients with ICH. We also suggest that serial serum cTnT assessment and long-term clinical outcome data from a large prospective study would clarify the clinical implications of elevated serum cTnT levels in patients with ICH.

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