Cardiac Troponin T Elevation After Stroke: Relationships Between Elevated Serum Troponin T, Stroke Location, and Prognosis

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Background and Purpose: Elevation of serum cardiac troponin T (cTnT) is regarded as a specific marker of acute coronary syndrome. Serum cTnT can be increased in patients with acute ischemic stroke, but its clinical implications remain unclear. The aim of this study was to identify the relationships between elevated cTnT and stroke severity, location, and prognosis.

Methods: From January 2005 to December 2006, this study recruited 455 consecutive patients who were admitted to Kangbuk Samsung Hospital due to acute ischemic stroke within 3 days of onset, which was confirmed by diffusion magnetic resonance imaging. A total of 416 patients was finally included and divided into 2 groups: an elevated cTnT group (n=45) and a normal cTnT group (n=371). The short-term prognosis was assessed by 30-day modified Rankin Scale responder analysis was compared between the two groups.

Results: Serum cTnT was elevated in 10.8% of cases, with elevated cTnT associated with greater stroke severity, as assessed by the National Institutes of Health Stroke Scale score, Insular-lobe involvement was more common in patients with elevated cTnT than in the normal cTnT group. Short-term prognosis was more unfavorable in the elevated cTnT group than in the normal cTnT group. Multivariate regression analysis indicated that elevated cTnT was independently related to insular involvement, cardioembolism, and unfavorable outcome.

Conclusions: Elevated cTnT in acute ischemic stroke was associated with severe neurological deficits at stroke onset and damages to the insular lobe. The outcome of acute ischemic stroke was worse for patients with elevated cTnT than for those with normal cTnT. The pathomechanism underlying acute ischemic stroke and subclinical myocardial damage warrants further study.

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Key Words: Serum cardiac troponin T (cTnT), Diffusion magnetic resonance imaging, Acute myocardial infarction (AMI), Stroke, Prognosis

INTRODUCTION

Stroke is one of major causes of death and disability in Western countries and in Korea. Due to the high mortality and morbidity rates associated with stroke, it is becoming a major community health problem worldwide. The association between heart

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disease and acute stroke is established.[1] Cardiac sequelae, including myocytolysis, serum enzyme elevation, and arrhythmia, are known to develop in some ischemic stroke patients.[2-6] The brain-heart connection was described early in the 20th century when Levy showed that changes in central nervous system metabolism influences cardiac function.[7] Several studies have found that the levels of creatinine kinase–MB fraction (CK-MB) and lactate dehydrogenase were elevated in 8-15% of patients with acute stroke,[8,9] and that elevated levels of serum troponin T are found in 10-34% of patients with acute stroke.[10-13] Serum cardiac troponin T (cTnT) is a new biochemical marker of myocardial damage with high specificity and sensitivity. There is considerable clinical and experimental evidence that cardiac changes in ischemic stroke result from excessive sympathetic nervous activity secondary to insular cortical damage.[14] Several mechanisms can result in elevated concentrations of serum cTnT during the early phase of ischemic stroke, such as primary myocardial damage with secondary cardioembolic cerebral ischemia or primary cerebral ischemia, with secondary myocardial injury attributable to central activation of the sympathoadrenal system.[9,15,16] Acute ischemic cerebrovascular events can induce various myocardial changes. Diffuse myocardial damage characterized by microislands of necrosis and subendocardial hemorrhage can occur after stroke.[8,17-21] This type of injury is called myocytolysis, and it occurs as a result of intense activation of the sympathetic nervous system. A potential primary focus of myocytolysis is presumed to be its extensive autonomic and limbic connection.[22,23]

The aims of our study were to (1) identify the relationship between elevated serum cTnT and stroke severity, (2) determine the relationship between elevated serum cTnT and insular involvement, and (3) elucidate the influence of elevated serum cTnT on the prognosis associated with ischemic stroke.

MATERIALS AND METHODS

We identified 455 consecutive patients from a stroke database who were admitted to Kangbuk Samsung Hospital with a diagnosis of ischemic stroke between January 2005 and December 2006. The inclusion criteria were (1) acute cerebral infarction confirmed by brain diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI) within 3 days of stoke onset; (2) measurement of serum cTnT level (≥0.01 ng/mL), and electrocardiography (ECG) and echocardiography performed within 3 days of stoke onset; and (3) a clear description of neurological scales. The exclusion criteria were (1) any recent ischemic heart disease, defined as previous myocardial infarction (AMI; American College of Cardiology/American Heart Association [ACC/AHA] criteria) within 2 weeks prior to and 3 days after stroke onset; (2) symptoms suggestive of AMI or unstable angina before admission; (3) newly developed pathologic Q waves on admission ECG; (4) previous coronary angioplasty or coronary bypass surgery; and (5) other heart diseases and debilitating diseases with the possibility of serum cTnT elevation, such as congestive heart failure, valvular heart disease (VHD), and end-stage renal disease (ESRD). The criteria for acute, evolving or recent AMI were defined by the ACC/AHA[24] as the elevation of biochemical markers of myocardial necrosis (preferably troponin) with at least one of the following: (1) ischemic symptoms, (2) development of pathologic Q waves on the ECG, (3) ECG changes indicative of ischemia (ST segment elevation [≥1 mm] or depression [≥0.5 mm]), and (4) coronary artery intervention (e.g., coronary angioplasty). Serum cTnT was measured as a part of routine laboratory testing on admission to exclude subclinical coronary events. The presence of intracerebral or subarachnoid hemorrhage was ruled out by computed tomography at the time of admission. Thus, the study population comprised patients with acute ischemic stroke but without known or overt new ischemic heart disease. Information regarding heart disease symptoms, cardiac history, and risk factors for cardiovascular disease were obtained from the patients' medical records. Serum cTnT was measured from venous blood samples using the Elecsys 2010 platform (Roche Diagnostics, Mannheim, Germany). The cut-off value for elevated serum cTnT was set at 0.01 ng/mL. Twelve-lead ECG was performed imme-

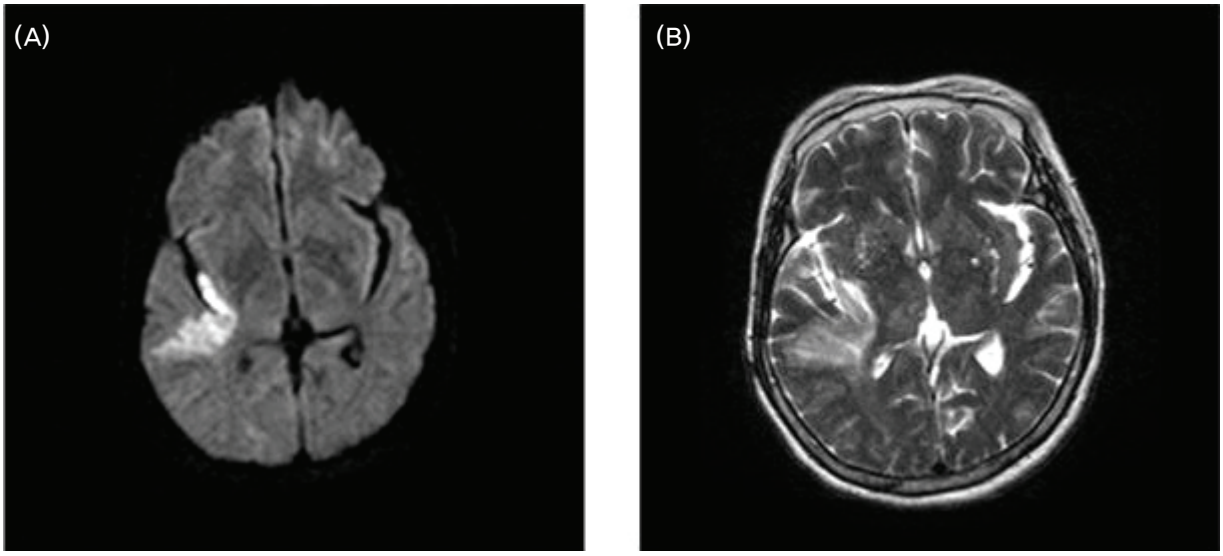

Figure 1. Diffusion-weighted magnetic resonance imaging (MRI) (A) and T_2-weighted MRI (B) of a 68-year-old woman, showing an ischemic stroke involving the right insular lobe.

diately on admission. Of the original cohort, 39 patients were excluded for the following reasons: diagnosis of transient focal neurologic deficits (7 patients), cTnT measurement performed after 3 days of stroke onset (9 patients), cardiac problems and debilitating medical disease (16 patients with AMI, 3 with VHD, and 2 with ESRD), and incomplete medical records (2 patients). Blood pressures and pulse rates were measured immediately upon presentation at the emergency room. MRI was performed on a 1.5-T whole-body scanner (Intera Zyroscan; Philips Medical System, The Netherlands). Single-shot echo planar DWI imaging was performed with a repeat time of 7,500 ms, an echo time of 99.3 ms, a field of view of 22×22 cm, matrix of 128×128 cm, a slice thickness of 5 mm with a 1-mm gap, 23 axial slices, and *b* values of 0 s/mm^2 and 1,000 s/mm^2, with 6 gradient directions and 3 averages. Acute cerebral infarction was characterized by regions of increased signal intensity on DWI and decreased signal intensity on apparent diffusion coefficient maps. Acute infarctions on DWI were outlined manually on a slice-by-slice basis by a neuroradiologist and neurologist who were blinded to the clinical data. Insular involvement was defined as regions that involved the right or left insular cortex (posterior, superior, and medial areas; Fig. 1). To evaluate the clinical outcome in each patient, we applied a responder analysis that defined favorable outcomes at 30 days (and not 90 days) as influenced by the baseline National Institutes of Health Stroke Scale (NIHSS). Favorable outcome was defined using the following criteria: a 30-day modified Rankin Scale (mRS) score of 0 if the baseline NIHSS score was <8, an mRS score of 0 or 1 if the NIHSS score was 8-14, and an mRS score 0-2 if the NIHSS score was >14.[25] Patients with an unfavorable outcome were defined as those not fulfilling the favorable-outcome criteria. The pathogenesis of stroke was classified by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[26,27]

Categorical and continuous variables were compared by the chi-square test and Student's *t*-test, respectively. Univariate and multivariate logistic regression was used for further analysis. The cut-off for statistical significance was set at p value of 0.05. Analyses were performed with SPSS for Windows (version 12.0, Chicago, IL, USA).

RESULTS

A total of 416 patients with acute stroke, as confirmed by DWI within 72 h of stroke onset, were enrolled

in this study. Serum cTnT was elevated in 10.8% (45/416) of the acute ischemic stroke patients. The 416 patients were divided into 2 groups according to serum cTnT levels: an elevated cTnT group (≥0.01 ng/mL) and a normal cTnT group (<0.01 ng/mL).

1. Comparison of the location and type of stroke between patients with elevated and normal serum cTnT

Epidemiologic and clinical characteristics were compared between the elevated and normal serum cTnT groups. Patients in the elevated serum cTnT group had a higher prevalence of atrial fibrillation and

Table 1. Epidemiologic and clinical characteristics of patients with elevated and normal serum cTnT

Variable	Elevated cTnT[a] (*n*=45)	Normal cTnT[a] (*n*=371)	*p*
Age (years)	72.46±5.37	66.07±4.82	0.058
Male	24 (53.3)	208 (56.1)	0.756
Time to admission (hours)	9.25±2.75	9.5±2.45	0.849
Medical history			
Hypertension	31 (68.9)	213 (57.4)	0.425
Diabetes mellitus	16 (35.6)	141 (38.0)	0.561
Atrial fibrillation	13 (28.9)	62 (16.7)	0.032*
Dyslipidemia	17 (37.8)	92 (24.8)	0.041*
Previous stroke history	10 (22.2)	72 (19.4)	0.659
Previous MI history	7 (15.6)	53 (14.3)	0.514
Current smoker	26 (57.8)	211 (56.9)	0.732
Pulse (beat/minute)	92.43±23.16	87.97±31.55	0.441
Systolic BP (mmHg)	168.82±22.13	159.65±25.23	0.326
Diastolic BP (mmHg)	106.51±8.33	110.74±20.36	0.517
Infarct location			
Right MCA territory	5 (11.1)	44 (11.9)	0.746
Left MCA territory	9 (20.0)	58 (15.6)	0.425
Insular involvement	13 (28.9)	56 (15.1)	0.042*
Right insular lobe	5 (11.1)	23 (6.2)	0.214
Left insular lobe	8 (17.8)	33 (8.9)	0.187
Bilateral ACA territory	2 (4.4)	7 (1.9)	0.091
Bilateral PCA territory	2 (4.4)	14 (3.8)	0.542
Deep penetrating infarction	8 (17.8)	138 (37.2)	0.041*
Brainstem	12 (26.7)	79 (21.3)	0.211
Cerebellum	2 (4.4)	26 (7.0)	0.497
Multiple territorial infarction	5 (11.1)	5 (1.3)	0.032*
TOAST classification			
Large-artery atherosclerosis	14 (31.1)	153 (41.2)	0.061
Cardioembolism	20 (44.4)	54 (14.6)	0.017*
Small-vessel occlusion	4 (8.9)	81 (21.8)	0.041*
Stroke of other determined etiology	0 (0)	8 (2)	0.132
Stroke of undetermined etiology	7 (15.6)	75 (20.2)	0.218

ACA; anterior cerebral artery, BP; blood pressure, MCA; middle cerebral artery, PCA; posterior cerebral artery, cTnT; serum cardiac troponin T, MI; myocardial infarction, TOAST; Trial of Org 10172 in Acute Stroke Treatment.
Statistical comparison between elevated and normal cTnT groups was performed only in each subset and the total study population.

[a]Data are *n* (%) or mean±SD values.

*Significant (p<0.05) difference between groups.

dyslipidemia than the normal serum cTnT group; they were also more likely to have multiple territorial infarctions and cardioembolism, but less likely to have deep penetrating artery infarction and, by TOAST classification, small vessel disease. Insular involvement was more common in the elevated serum cTnT group

Table 2. Comparison of the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores between patients with elevated and normal serum cTnT

Variable	Elevated cTnT (*n*=45)	Normal cTnT (*n*=371)	*p*
NIHSS score			
Admission	11 (8-38)	9 (6-22)	
Day 7	9 (6-29)	8 (4-20)	
Day 30	8 (7-18)	5 (3-14)	
mRS			
Day 1	4 (2-5)	3 (2-5)	
Day 7	3 (2-5)	2 (1-4)	
Day 30	3 (1-4)	2 (1-4)	
Favorable outcome†	3/45 (6.7%)	72/371 (19.4%)	0.015*
Unfavorable outcome†	42/45 (93.3%)	299/371 (80.5%)	0.036*

Values are medians and interquartile ranges.

*Significant (p<0.05) difference between groups.

†Defined according to 30-day mRS responder analysis.

Table 3. Univariate analysis for variables associated with elevated serum cTnT

Variables	Odds ratio (95% confidence interval)	*p*
Age (per 5.2 years)	1.21 (0.82–1.63)	0.133
Sex (male)	0.86 (0.66–1.49)	0.253
Time to admission (1.7 hours)	0.64 (0.31–1.04)	0.341
Pulse (per 12.1/minute)	1.07 (0.61–1.51)	0.337
Systolic BP (per 10.9 mmHg)	1.29 (0.75–1.82)	0.175
Diastolic BP (per 8.0 mmHg)	1.16 (0.64–1.65)	0.251
Infarct location (presence)		
Right MCA territory	0.85 (0.46–1.24)	0.129
Left MCA territory	0.76 (0.39–1.17)	0.242
Insular involvement	2.83 (2.11–3.52)	0.021*
Right Insular lobe	1.22 (0.72–1.89)	0.189
Left Insular lobe	1.47 (0.95–1.96)	0.147
Brainstem	1.85 (1.15–2.46)	0.038*
Multiple territorial infarction	1.74 (1.01–2.35)	0.047*
TOAST classification		
Large-artery atherosclerosis	1.86 (1.17–2.49)	0.045*
Cardioembolism	2.71 (2.23–3.25)	0.011*
Small-vessel occlusion	0.96 (0.46–1.23)	0.306
Stroke of undetermined etiology	0.78 (0.35–1.24)	0.494
Unfavorable outcome†	2.63 (1.74–3.41)	0.016*

Continuous variables like age, time to admission, pulse, systolic blood pressure, and diastolic blood pressure were categorized according to their standard deviation values during logistic regression analysis (Age: 5.2 years, Time to admission: 1.7 hours, pulse: 12.1/minute, systolic BP: 10.9 mmHg, diastolic BP: 10.9 mmHg).

*Significant (p<0.05) difference between groups.

†According to 30-day mRS responder analysis.

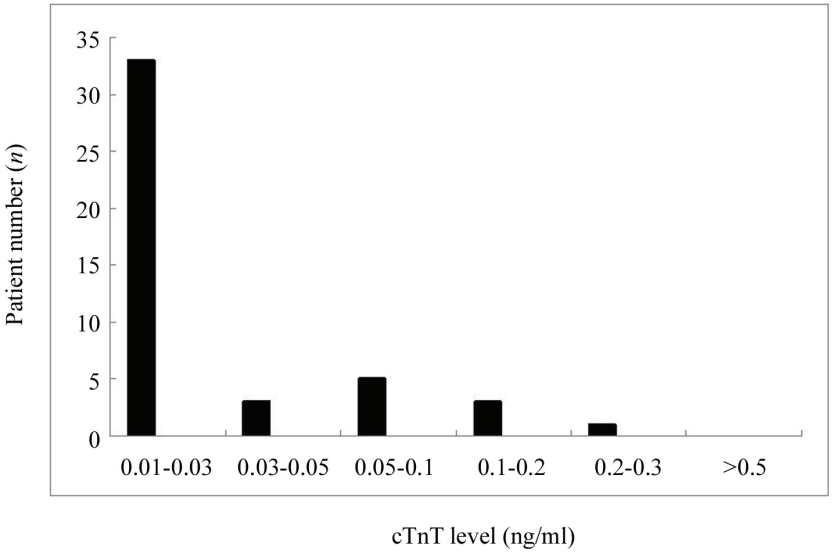

Figure 2. Levels of serum cardiac troponin T (cTnT in the elevated cTnT group, *n*=45).

than in the normal serum cTnT group (56/371 [15.1%] vs. 13/45 [28.9%], *p*=0.042), but hemispheric laterality of insular involvement was not evident (Table 1).

2. Comparison of severity and prognosis between patients with elevated and normal serum cTnT

We compared stroke severity using the criterion of NIHSS score on the 1st day of admission. The stroke severity in the elevated serum cTnT group was greater and the disability was more severe (mRS on the 1st day) than in the normal serum cTnT group. The short-term prognosis (30 days) was estimated by comparing the improvement using 30-day mRS responder analysis.[25] The outcome was more favorable in the elevated serum cTnT group than in the normal serum cTnT group (3/45 [6.7%] vs. 72/371 [19.4%], *p*=0.015; Table 2). The univariate analysis showed that the elevated serum cTnT group was significantly associated with insular-lobe involvement, brainstem infarction, multiple territorial infarctions, cardioembolism and large-artery atherosclerosis, and unfavorable outcome (Table 3). Separate analysis of those variables identified in the univariate analysis for the independent association with elevated serum cTnT by multivariate analysis indicated that only insular-lobe involvement, cardio-embolic stroke and unfavorable outcome were indepen-dently related to elevated serum cTnT (Table 4).

Table 4. Multivariate analysis for variables independently associated with elevated serum cTnT

Variables	Odds ratio (95% confidence interval)	*p*
Location		
Insular involvement	2.59 (1.89–3.16)	0.034*
Brain-stem	1.62 (1.15–2.24)	0.063
Multiple territorial infarction	1.48 (0.78–1.99)	0.059
Large-artery atherosclerosis	1.42 (0.85–2.02)	0.072
TOAST classification		
Cardioembolism	2.51 (1.77–3.19)	0.037*
Unfavorable outcome†	2.42 (1.89–2.96)	0.025*

*Significant ($p<0.05$) difference between groups.
†According to 30-day mRS responder analysis.

Levels of serum cTnT were less than 0.1 ng/mL in 91.1% of patients in the elevated cTnT group; they were more than 0.1 ng/mL in four (8.9%) of these patients, and the highest serum cTnT level in this group was 0.266 ng/mL (Fig. 2). Abnormalities on cardiologic evaluations including ECG, serum CK-MB, and echocardiogram were more frequent in the elevated serum cTnT group than in the normal serum cTnT group (Table 5).

DISCUSSION

Elevated serum cTnT was detected in 10.8% of the acute ischemic stroke patients that we examined, and was related to unfavorable outcomes 30 days after ischemic stroke. One of the novel findings of this study is that elevated serum cTnT in patients with ischemic stroke might be associated with stroke location and unfavorable outcome.

Every stroke is likely to exert considerable stress on the patient's heart. Elevated serum cTnT might be indicative of a lower cardiac tolerance to stress caused by the acute ischemic stroke. This is possible explanation for the relationship between elevated serum cTnT and the poor short-term prognosis found in this study. Previous studies have suggested that cardiac damage after ischemic stroke is associated with sympathoadrenal activation.[14,20] Epinephrine and cortisol concentrations are elevated after a stroke and higher concentrations have been reported in association with myocardial damage.[10] In the present study, elevated serum cTnT level was associated with severe stroke and insular-lobe damage, regardless of laterality, which can cause severe stress and lead to sympathoadrenal activation.

This study demonstrates that there is a relationship between elevated serum cTnT and stroke with insular cortex involvement. Sensory, autonomic, and limbic functions are integrated in the insula through reciprocal connections with principle sensory areas, paralimbic areas in the orbital, temporopolar and cingulate cortices, and the hypothalamus. Stimulation of the insula in rats as well as in humans undergoing surgery for epilepsy has demonstrated that this brain area is involved in cardiac autonomic control.[13,28,29] The short-term outcome is less favorable and the stroke is more severe in stroke patients with elevated serum cTnT than in those with normal serum cTnT levels. Cardioembolic stroke was more common in patients with elevated serum cTnT. Doctors in charge of stroke units should be more prudent when dealing with these patients and should offer cardiologic evaluations and secondary

Table 5. Abnormal findings on cardiologic evaluations in the elevated and normal serum cTnT groups

	Elevated cTnT[a] (*n*=45)	Normal cTnT[a] (*n*=371)	*p*
Electrocardiogram[†]			
> 1 mm ST depression	5 (11.1)	21 (5.7)	0.024*
> 0.5 mm ST elevation	0 (0)	0 (0)	
Pathologic Q wave	3 (6.6)	0 (0)	0.019*
Increased cardiac enzyme CK-MB	25 (55.6)	22 (5.9)	0.011*
Echocardiogram			
Focal wall hypokinesia	6 (13.3)	0 (0)	0.006*
Global hypokinesia	2 (4.4)	0 (0)	0.008*
Decreased ejection fraction	9 (20.0)	12 (3.2)	0.042*

[a]Data are *n* (%) values.

*Significant ($p<0.05$) difference between groups.

Statistical comparison between elevated and normal cTnT groups was performed only in each subset and the total study population.

[†]According to ACC/AHA guidelines, ≥ 0.5-mm ST depression or ≥ 1-mm ST elevation in two or more contiguous leads was defined as an electrical abnormality. CK-MB, serum creatine kinase MB.

prevention measures, and also investigations for stroke risk factors and proper interventions for coronary artery disease. When excluding patients with obvious cardiac damage from the study population, patients in the elevated serum cTnT group (0.16±0.15 μg/L, mean±SD) did not satisfy the clinical, ECG or echocardiographic criteria for AMI (ACC/AHA criteria). The ST segment elevations and depressions were not prominent enough to meet the criteria for AMI as defined by the ACC/AHA. Two of patients had developed pathologic Q waves since their previous ECG, which had been taken more than 6 months before that performed for the current study. None of the patients in the elevated serum cTnT group had chest pain. These findings might be attributable to serum cTnT being a more sensitive for indicator of myocardial damage. However, the elevation of serum cTnT might be related to underlying coronary artery disease exacerbated by the stress of an acute ischemic stroke. Our study was subject to several limitations. First, we relied on single baseline blood samples and did not retest serum cTnT so as to determine trends in the cTnT level, and thus we were unable to account for variations in serum cTnT levels that might have occurred over time. Repeated assays could provide additional information on the development and evolution of myocardial damage in patients with acute ischemic stroke. Second, we did not measure the concentrations of epinephrine, norepinephrine and cortisol as indirect markers of sympathoadrenal activation, which might have provided further information on the tone of the sympathetic nervous system. Third, our study was unable to assess the long-term prognosis in normal and elevated serum cTnT groups due to the short follow-up period. Despite these limitations, the findings of this study will improve the understanding of the implications of serum cTnT elevation in acute ischemic stroke. We suggest that clinicians should consider adding a serum cTnT titer to their routine admission testing in patients with suspected ischemic stroke, since a high serum cTnT level appears to be related to a significantly higher risk for worse outcomes and cardiac complications. Information on serum cTnT might also provide clues as to the location and extent of ischemic stroke.

In summary, elevated serum cTnT concentration without evidence of myocardial lesion was found in 10.8% of the acute ischemic stroke patients that we examined. Stroke severity (as assessed by the NIHSS and mRS) and insular-lobe involvement were associated with increased serum cTnT levels. Patients with elevated serum cTnT levels during acute ischemic stroke treatment showed worse outcomes than those with normal serum cTnT levels. Serial serum cTnT assessment and long-term clinical outcome data in a larger study population are needed in future studies in order to clarify the clinical implications of elevated serum cTnT levels in acute ischemic stroke.

REFERENCES

1. James P, Ellis CJ, Whitlock RM, McNeil AR, Henley J, Anderson NE. Relation between troponin T concentration and mortality in patients presenting with an acute stroke: observational study. *BMJ* 2000;320:1502-1504.
2. Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* 1994;90:195-203.
3. Inoue S, Murakami Y, Sano K, Katoh H, Shimada T. Atrium as a source of brain natriuretic polypeptide in patients with atrial fibrillation. *J Card Fail* 2000;6:92-96.
4. Takahashi K, Totsune K, Sone M, Ohneda M, Murakami O, Itoi K, et al. Human brain natriuretic peptide-like immunoreactivity in human brain. *Peptides* 1992;13:121-123.
5. Wijdicks EF, Schievink WI, Burnett JC Jr. Natriuretic peptide system and endothelin in aneurysmal subarachnoid hemorrhage. *J Neurosurg* 1997;87:275-280.
6. Sviri GE, Feinsod M, Soustiel JF. Brain natriuretic peptide and cerebral vasospasm in subarachnoid hemorrhage: clinical and TCD correlations. *Stroke* 2000;31:118-122.
7. Levy A. The exiting causes of ventricular fibrillation in animals under chloroform anesthesia. *Heart* 1913;4:319-78.
8. Norris JW, Hachinski VC, Myers MG, Callow J, Wong T, Moore RW. Serum cardiac enzymes in stroke. *Stroke*

1979;10:548-553.
9. Myers MG, Norris JW, Hachinski VC, Weingert ME, Sole MJ. Cardiac sequelae of acute stroke. *Stroke* 1982;13:838-842.
10. Christensen H, Johannesen HH, Christensen AF, Bendtzen K, Boysen G. Serum cardiac troponin I in acute stroke is related to serum cortisol and TNF-alpha. *Cerebrovasc Dis* 2004;18:194-199.
11. Trooyen M, Indredavik B, Rossvoll O, Slordahl SA. Myocardial injury in acute stroke assessed by troponin I. *Tidsskr Nor Laegeforen* 2001;121:421-425.
12. Di Angelantonio E, Fiorelli M, Toni D, Sacchetti ML, Lorenzano S, Falcou A, et al. Prognostic significance of admission levels of troponin I in patients with acute ischaemic stroke. *J Neurol Neurosurg Psychiatry* 2005; 76:76-81.
13. Ay H, Koroshetz WJ, Benner T, Vangel MG, Melinosky C, Arsava EM, et al. Neuroanatomic correlates of stroke-related myocardial injury. *Neurology* 2006;66:1325-1329.
14. Barber M, Morton JJ, Macfarlane PW, Barlow N, Roditi G, Stott DJ. Elevated troponin levels are associated with sympathoadrenal activation in acute ischemic stroke. *Cerebrovasc Dis* 2007;23:260-266.
15. Etgen T, Baum H, Sander K, Sander D. Cardiac troponins and N-terminal pro-brain natriuretic peptide in acute ischemic stroke do not relate to clinical prognosis. *Stroke* 2005;36:270-275.
16. Klingelhöfer J, Sander D. Cardiovascular consequences of clinical stroke. *Baillieres Clin Neurol* 1997;6:309-335.
17. Connor RC. Heart damage associated with intracranial lesions. *Br Med J* 1968;3:29-31.
18. Weidler DJ. Myocardial damage and cardiac arrhythmias after intracranial hemorrhage. A critical review. *Stroke* 1974;5:759-764.
19. Jacob WA, Van Bogaert A, De Groodt-Lasseel MH. Myocardial ultrastructure and haemodynamic reactions during experimental subarachnoid haemorrhage. *J Mol Cell Cardiol* 1972;4:287-298.
20. Raab W, Stark E, Macmillan WH, Gigee WR. Sympathogenic origin and antiadrenergic prevention of stress-induced myocardial lesions. *Am J Cardiol* 1961;8:203-211.
21. Oppenheimer SM, Wilson JX, Guiraudon C, Cechetto DF. Insular cortex stimulation produces lethal cardiac arrhythmias: a mechanism of sudden death? *Brain Res* 1991;550:115-121.
22. Oppenheimer SM, Cechetto DF. Cardiac chronotropic organization of the rat insular cortex. *Brain Res* 1990; 533:66-72.
23. Cechetto DF, Wilson JX, Smith KE, Wolski D, Silver MD, Hachinski VC. Autonomic and myocardial changes in middle cerebral artery occlusion: stroke models in the rat. *Brain Res* 1989;502:296-305.
24. Alpert JS, Thygesen K, Antman E, Bassand JP. Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined-a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000 Sep;36(3):959-69.
25. Adams HP Jr, Leclerc JR, Bluhmki E, Clarke W, Hansen MD, Hacke W. Measuring outcomes as a function of baseline severity of ischemic stroke. *Cerebrovasc Dis* 2004;18:124-129.
26. Advisory Council for the National Institute of Neurological Diseases and Blindness. A classification and outline of cerebrovascular diseases. *Neurology* 1958;8: 395-434.
27. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24:35-41.
28. Yasui Y, Breder CD, Saper CB, Cechetto DF. Autonomic responses and efferent pathways from the insular cortex in the rat. *J Comp Neurol* 1991;303:355-374.
29. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. *Neurology* 1992;42:1727-1732.