Relation Between Cardiac Troponins And In-Hospital Mortality In Right-Sided Stroke Patients

Sağ tutulumlu iskemik inmelerde hastane içi mortalite ve kardiyak troponinler arasındaki ilişki

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SUMMARY

Objectives: The association between acute ischemic strokes and cardiovascular disturbances has been established previously. The insula of the right cerebral hemisphere may have a major role in cardiac autonomic control. We investigated if elevated troponin T (cTnT) and troponin I (cTnI), the specific biomarkers of cardiac damage, are independent predictors of in-hospital mortality in right-sided stroke patients.

Materials and Methods: Sixty-six patients with acute ischemic right hemispheric involvement who were admitted to a university hospital during an eight-month period were included in this prospective observational clinical study. The levels of cardiac biomarkers were measured and compared with the in-hospital mortality rates.

Results: Hospital mortality was significantly higher in patients with cTnT>0.1 ng/ml (4 [44.4%] vs 5 [8.8%]; p=0.016) but not in patients with cTnI>1.5 ng/ml (3 [33.3%] vs 6 [10.5%]; p=0.098). Initial National Institute of Health Stroke Scale (NIHSS) scores and Glasgow Coma Scale scores were also significantly higher in patients who were dead in-hospital (median: 16 vs 6; p=0.00, and median: 11 vs 15; p=0.007, respectively). Logistic regression analysis have revealed that elevated cTnT values and NIHSS scores at admission were independent predictors of death in-hospital (p=0.04, [OR 0.03, 95% CI 0.0-0.8]; p=0.046, [OR 2.8, 95% CI 1.082-7.433, respectively).

Conclusion: We conclude that elevated CTnT, but not CTnI, may be an independent predictor of in-hospital mortality in acute ischemic right-sided stroke patients.

Key words: Cardiac troponin; mortality; right-sided stroke.

ÖZET

Giriş: *Akut iskemik inme ve kardiyovasküler sistemde meydana gelen değişiklikler arasındaki ilişki daha önce kanıtlanmıştı. Sağ serebral heminsferde bulunan insula, kalbin otonomik kontrolünde önemli rol oynar. Bu çalışmada kardiyak hasarın belirteçleri olan troponin T (cTnT) ve troponin I'nın (cTnI) sağ serebral heminsfer inmelerinde hastane içi mortaliteyi tahmin etmedeki etkinliklerini belirlemeyi amaçladık.*

Gereç ve Yöntem: *İleriye dönük olarak sekiz aylık periyotta bir üniversite hastanesinde gerçekleştirilen bu çalışmaya sağ heminsferden kaynaklanan iskemik inme nedeniyle başvuran 66 hasta alındı. Kardiyak belirteç seviyeleri belirlenerek hastane içi mortalite ile ilişkisine bakıldı.*

Bulgular: *Hastane içi mortalite cTnT >0,1 ng/ml (4 [%44,4] ve 5 [%8,8]; p=0,016) olan hastalarda anlamlı olarak yüksek iken, cTnI >1,5 ng/ml (3 [%33,3] ve 6 [%10,5]; p=0,098) olan hastalarda mortalite oranı yüksek olmasına rağmen istatistiksel anlamlılık saptanmadı. Hastanede ölen hastalarda başlangıç National Institute of Health Stroke Scale (NIHSS) ve Glasgow Coma Scale skorları anlamlı olarak daha yüksekti (median: 16 ve 6; p=0,00, ile median: 11 ve 15; p=0,007, sırasıyla). Lojistik regresyon analizinde başlangıçtaki cTnT ve NIHSS skoru hastane içi mortaliteyi belirlemede istatistiksel olarak anlamlı bağımsız değişkenler olarak saptandı (p=0,04, [OR 0,03, %95 CI 0,0-0,8]; p=0,046, [OR 2,8, %95 CI 1,082-7,433], sırasıyla).*

Sonuç: *Sağ serebral heminsferden kaynaklanan inme nedeniyle başvuran hastalarda cTnT hastane içi mortaliteyi belirlemede anlamlı iken aynı anlamlılık cTnI için geçerli değildir.*

Anahtar sözcükler: *Kardiyak troponin; mortalite; sağ heminsferden kaynaklanan inme.*

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Introduction

Acute stroke is a neurological emergency characterized by the sudden loss of circulation to an area of the brain, resulting in a corresponding loss of neurological function and one of the major causes of long term morbidity and mortality. Cardiac biomarkers may increase in some patients with acute stroke as a result of cardiac damage due to autonomic dysfunction of sympthatetic cardiovascular tone.[1-5] On the other hand, some others found no correlation between cardiac troponins and outcomes following stroke.[6]

We aimed to assess whether raised cardiac troponin concentrations would be independent predictors of mortality in patients with an acute ischemic right-sided stroke.

Methods

Consecutive 89 patients with an acute right hemispheric cerebral infarction within 24 hours after the onset of symptoms composed our study sample. During a six-month period, all stroke patients who were presented to the Emergency Department were included in the study after the Hospital Review Board's approval. The informed consent for the study was obtained from the patients or from their relatives unless communication is optimal.

We prospectively collected the patients' data in terms of the demographic characteristics such as gender, age, co-existing illness (hypertension, diabetes, coronary artery diseases, renal diseases, etc.), and smoking habits, initial blood pressures, pulse rates, The National Institutes of Health Stroke Scale (NIHSS) scores, and Glasgow Coma Scale (GCS) scores of the patients were recorded. NIHSS and GCS were obtained on admission and performed by experienced examiners. Also, initial electrocardiography (ECG), chest X-ray, head computerized tomography, blood glucose, blood urine nitrogen (BUN), creatine kinase (CK), and creatine kinase-myocardial band (CK-MB) were ordered for all patients at admission. Blood samples for measuring cTnT and cTnI concentrations were collected in 18-24 hours after admission; serum samples were frozen at -70°C unless the assay was completed within 4 hours. CTnT was measured by electrochemiluminescence method (Roche Diagnostics, Switzerland using Elecys-2010 systems) and cTnI levels were measured by chemiluminescence method (Chiron Diagnostics, USA using CIBA-Corning, ACS-180 Analyzer). Serum concentrations over 0.1 ng/ml for cTnT and over 1.5 ng/ml for cTnI were accepted as elevated results.[7] All patients with suspected acute stroke were ordered head computerized tomography during emergency department management and test results were interpreted by a radiologist. Patients with diagnostic radiological findings of acute cerebral right cerebral hemispheric infarction were included. Patients with symptoms mimicking right-sided stroke but without an evidence of a computerized head tomography interpretation by a radiologist were excluded. None of the patients received thrombolytic therapy neither in emergency department nor during their hospital course. Primary end point was in-hospital mortality in 30 days for this study. In-hospital deaths due to neurological causes (due to complication of the stroke) were also included.

Statistical analysis of the results was calculated by SPSS v11.0 for Windows, and student t-test Fisher exact test and Mann-Whitney U-test were used for the statistical analysis. All the hypotheses were constructed two tailed and a p value of ≤ 0.05 was accepted as significant.

Results

Eighty-nine patients with acute ischemic right-sided stroke met the inclusion criteria during the study period. Eleven patients without radiological confirmation, eight patients who were lost to follow-up (transferred to another hospital) and four patients with inadequate chart data (failure to obtain initial blood tests for cardiac biomarkers) were excluded from the study. Sixty-six patients with acute ischemic right-sided stroke admitted to our prospective observational clinical study.

Demographics

There was no difference between the population mean ages of the males and females (respectively, 70±9.17 vs 69±10.08; p=0.841). Of 66 patients admitted to the neurology clinic, nine (13.6%) patients died during their hospital course. There was no any significant relation between dead and discharged patients according to their demographic data.

Physical Examination and Laboratory Tests

Physical examination and laboratory findings were insignificant but initial NIHSS and GCS scores. Initial NIHSS scores and GCS scores between patients who were dead in-hospital and discharged from the hospital were statistically significant (median: 16 vs 6; p=0.00, and median: 11 vs 15; p=0.007, respectively).

Troponin T

Cardiac TnT concentrations were raised (mean, 0.696 ± 0.62 ng/ml) in nine (13%) of 66 patients. Baseline characteristics of patients with elevated and normal cTnT values at ED presentation were shown at Table 1.

According to baseline characteristics mean age, total CK values, CK-MB values, NIHSS and GCS scores were statistically significant in elevated CTnT group (p=0.014, p=0.024, p=0.02, 0.003, 0.011 respectively). Cardiac TnT elevations were statistically significant in-hospital deaths. Also among the patients with higher cTnT concentrations than 0.1 ng/ml, mean cTnT concentration was higher in-hospital deaths according to discharged patients (Table 2, p=0.016).

Troponin I

Cardiac TnI concentrations were raised (mean, 13.95± 16.72) ng/ml) in nine (13%) of 66 patients. Baseline characteristics of patients with elevated cTnI at emergency department presentation were shown at Table 3.

According to baseline characteristics mean age, CK-MB values, NIHSS and GCS scores were statistically significant in elevated cTnI group (p=0.021, p=0.02, 0.024, 0.001 respectively). Although mean cTnI concentration was higher in patients who died in-hospital according to patients who were discharged, mean cTnI concentration was statistically insignificant among in-hospital deaths (Table 4, p=0.098).

Table 1. *Baseline characteristics at Emergency Department presentation for Tn T.*

Characteristics at Emergency Department presentation		Troponin T (ng/ml)		Significance (p<0.05)
		<0.1	≥0.1	
Total		57 (86%)	9 (13%)	
Demographics	Age (mean)	69±9.4	77±7.6	**0.014** [a]
	Male	29 (50%)	4 (45%)	1 [b]
	Female	28 (50%)	5 (55%)	1 [b]
Risk factors for ACS	Hypertension	35 (62.5%)	5 (55.6%)	0.730 [c]
	Diabetes	20 (35%)	2 (22.2%)	0.706 [c]
	Smoking	14 (25%)	3 (33.3%)	0.709 [c]
	History of CAD	26 (46.4%)	6 (66.6%)	0.220 [c]
Past medical history	Acute coronary syndrome	1 (1.7%)	1 (11.1%)	0.256 [c]
	Transient ischemic attack	8 (14.2%)	0	0.586 [c]
Vital signs at any time in Emergency Department	Sys BP >180 mmHg	12 (21.4%)	0	0.131 [b]
	Dia BP >110 mmHg	10 (17.9%)	0	0.176 [b]
	Respiratory Rate >20	32 (57.1%)	5 (55.5%)	1 [c]
	Pulse <60 or >100	15 (26%)	4 (44.4%)	0.267 [c]
Lab values at admission	Total CK >200 U/L	6 (10.7%)	4 (44.4%)	**0.024** [c]
	CK-MB >25 U/L	19 (33.9%)	8 (88.8%)	**0.02** [c]
	Creatinine >1.5 mg/dl	11 (64.7%)	6 (35.3%)	0.07 [c]
	Glucose >110 mg/dl	46 (82.1%)	7 (77.8%)	1 [c]

a: Student-t test; b: Mann Whitney U-test; c: Fisher exact test.

Table 2. *Number of patients died in hospital or discharged according to Tn T elevations.*

Tn T (ng/ml)	Number of patients died in hospital	Number of patients discharged	Total
<0.1	5 (8.8%) [a]	52 (91.2%) [a]	57
	(mean 0.01±0.00)	(mean 0.01±0.015)	(mean, 0.014±0.01)
>0.1	4 (44.4%) [a]	5 (55.6%) [a]	9
	(mean 0.36±0.28)	(mean 0.96±0.71)	(mean, 0.696±0.62)
Total	9 (13.6%) [a]	57 (86.4%) [a]	66

p=0.016, Likelihood ratio=6.3, a row percentages.

Outcome

Six factors that may predict death were assessed in a multivariate model. The post-hoc logistic regression analysis of age, coronary artery disease, hypertension, cTnT values, GCS scores at admission and NIHSS scores have revealed that cTnT values and NIHSS scores at admission were independent predictors of death in-hospital (p=0.04, [OR 0.03, 95% CI 0.0-0.8]; p=0.046, [OR 2.8, 95% CI 1.082-7.433 respectively). There were no any statistically correlations between two groups of subjects in terms of cardiac arrhythmias, cigarette smoking, renal insufficiency and transient ischemic attack when we applied the post-hoc logistic regression analysis to other factors may predict in-hospital mortality.

Discussion

The most common cause of death is cardiovascular disease in acute stroke patients.[8] Relationship between stroke outcome and several factors such as age, serum cortisol, inflammatory markers, atherosclerotic profile, low GCS score, NIHSS score, localization of the infarct area, antithrombin III levels and region of the stroke particularly in the right insula have been reported previously.[9-18] Recently, several reports have been focused on predictive value of cardiac biomarkers in patients with stroke. Elevations in serum concentrations of cardiac troponins may indicate a subtle cardiovascular disease in stroke patients and an increase in mortality. In a recent study, it was concluded that patients with right hemispheric ischemic lesions are likely to have cardiac disturbances.[19] It was concluded that the right insula especially plays a significant role in central autonomic sympathetic cardiovascular control.[18,20] Hence, it is suggested that right middle cerebral artery infarction disinhibits insular function, resulting in increased sympathetic cardiovascular tone and the cardiac consequences of stroke.[21] These findings may explain

Table 3. *Baseline characteristics at Emergency Department presentation for Tn I.*

Characteristics at Emergency Department presentation		Troponin I (ng/ml)		p
		<1.5	≥1.5	
Total		57 (86%)	9 (13%)	
Demographics	**Age** (mean)	69±9.3	77±8.8	**0.021** [a]
	Male	27 (47.4%)	6 (66%)	1 [b]
	Female	30 (52.6%)	3 (33%)	1 [b]
Risk factors for ACS	Hypertension (+)	35 (61.4%)	5 (55%)	0.730 [c]
	Diabetes	20 (35.1%)	2 (22%)	0.706 [c]
	Smoking	15 (26.3%)	3 (33%)	0.709 [c]
	Past history of CAD	24 (42.1%)	5 (55%)	0.220 [c]
Physical findings in Emergency Department	Sys BP >180 mmHg	8 (14%)	1 (11%)	1 [c]
	Dia BP >110 mmHg	9 (15.8%)	1 (11%)	1 [c]
	RR >20	30 (52.6%)	6 (66%)	0.436 [c]
	Pulse <60 or >100	14 (19.3%)	4 (44%)	0.106 [c]
Lab values at admission	Total CK >200 U/L	7 (12.2%)	3 (33%)	0.130 [c]
	CK-MB >25 U/L	20 (35%)	7 (77.7%)	**0.02** [c]
	Creatinine >1.5 mg/dl	9 (15.8%)	3 (33%)	0.220 [c]
	Glucose >110 mg/dl	46 (80%)	8 (89%)	1 [c]

a: Student-t test; b: Mann Whitney U-test; c: Fisher exact test.

Table 4. *Number of patients died in hospital or discharged according to Tn I elevations.*

Tn I (ng/ml)	Number of patients died in hospital	Number of patients discharged	Total
<1.5	6 (10.5%) [a]	51 (89.4%) [a]	57
	(mean 0.22±0.13)	(mean 0.18±0.13)	(mean, 0.18±0.13)
>1.5	3 (33.3%) [a]	6 (66.6%) [a]	9
	(mean 11.9±9.0)	(mean 14.9±20.2)	(mean, 13.95±16.72)
Total	9 (13,6%) [a]	57 (86,4%) [a]	66

p=0.098, a row percentages.

the relationship between stroke and cardiac disturbances so that increased sympathoadrenal tone might be the major cause of neurogenic cardiac damage as a result of damage to cortical areas involved in cardiac and autonomic control.

Also, no relation to morbidity and mortality was found for cTnT and cTnI in 174 patients by Etgen et al. They reported that lesion size, insular involvement, sex, age, and stroke severity had significant impact on the outcome instead of elevations of cardiac troponins in their study.

On the other hand, James et al. reported that cTnT concentration at hospital admission was a powerful predictor of mortality in 181 stroke patients.[22] Moreover, a positive correlation between serum levels of cTnT and stroke volume was reported in a recent study.[4] However the mains of that study were to investigate predictive value of cTnT in assessing myocardial injury and cardiac dysfunctions in different types of stroke so that they could not make a conclusion on the relation between cTnT concentrations and mortality.

Christensen et al. reported that elevations of cTnI concentrations were positive in 35% of all stroke patients and 63% of 155 patients died within 3 months and cTnI positivity was, together with age, stroke severity and prestroke modified Rankin scale an independent explanatory variable of outcome at 3 months (death or dependency).[23] In another cohort study, Di Angelantonio et al. reported that high cTnI levels seem to impart a significantly higher risk of in-hospital cardiac complications and death.[5] They found that there was a distinctive prognostic gradient in 330 patients among three cTnI groups (as lower than 0.10 ng/ml, low positive and high positive) with mortality increasing with cTnI levels.

In the literature, studies with relatively larger sample size tend to show a strong relationship between high troponin concentrations and mortality. In our study, with 66 right-sided hemispheric stroke patients we found that cTnT concentrations were significantly higher in patients died in-hospital according to discharged from the hospital. However, no correlation was found with cTnI and in-hospital mortality in the same population. The most explanatory reason is our relatively small study sample size to demonstrate a relation between cTnI and in-hospital mortality. The further studies with much larger sample size are needed to demonstrate more powerful relationship between cardiac disturbances and in-hospital mortality in right-sided stroke patients.

On the other hand, the other cardiac biomarkers, CK and CK-MB were significantly higher in patients with elevated cTnT concentrations while only CK-MB was significantly higher in patients with elevated cTnI concentrations in our study. Ay et al. concluded that cTnT did not exceed the reference range in any stroke patients and therefore elevations in CK-MB in stroke patients might be out-of-heart origin.[24] However they investigated a relatively small number of patients who were grouped according to their cerebral infarctions involving regions in the territory of middle, anterior, or posterior cerebral arteries, instead of grouping right or left hemispheric ischemia and of 32 total patients, only 24 patients had middle cerebral artery occlusion. Although Ay et al. suggested that elevations of CK-MB without concomitant cTnT elevations were likely to be from noncardiac origins in acute hemispheric strokes, it is a subject to debate the origin of CK and CK-MB elevations according to our results. In the current literature, in respect of their results, it was suggested that right or left territory of middle cerebral arteries differ in cardiac autonomic dysfunction where right insular cortex is likely responsible for cortical regulation of cardiac sympathetic activity and left insular cortex is likely responsible for cardiac parasympathetic activity.[19,22,25,26]

In the light of these evidences, it is likely to suggest that ischemic stroke, involving the right hemisphere, induces cardiac damage by nonischemic mechanisms. None of our patients had declared any symptoms suggesting they were suffering a myocardial ischemia before they had stroke attack. Although the serial ECGs were nondiagnostic during hospital course, echocardiographic follow up might be needed to reveal cardiac damage. On the other hand other factors such as renal failure that might make elevations in troponin levels were followed up during the hospital course.

The present study has inevitable limitations. First, the main weakness of our study is the small amount of patients especially in-hospital mortality group. Relatively small number of patients in subgroups has limited our results. Especially we could not make a multivariate stepwise model with over six factors because of limited patient number so that we have to analyze our variables in a post hoc regression analysis. Second, the difference between the cTnT concentrations were small so that using student t-test results were insignificant but when we accepted cTnT concentrations as “high” or “low” according to 0.1 ng/dl cut off point, and using Fisher exact test we had the significant relationship.

Also, both cTnT and cTnI levels were obtained only as a single measurement and so that we could only make conclusion about initial elevated values instead of alterations during hospital course. Third, our hospital policies did not include thrombolytic agents for stroke patients so that none of the patients had had t-PA therapy during the study protocol. Currently, implementation of thrombolytic agents in stroke management has changed the clinical outcomes of the patients.[27] The results of our study may be valuable when investigating the role of troponins as mortality predictors during the comparison with the studies in the era of thrombolytics. Also, the interpretation of head computerized tomography images was done by one senior radiologist and we could not investigate the interpreters' reliability. Finally, we investigated only right-sided hemispheric stroke patients and neither estimated the stroke volume according to computerized tomography images nor compared with left-sided strokes. Further studies comparing right and left sided strokes are needed to explain the role of cardiac biomarkers in cardiac consequences of stroke.

We conclude that our clinical study demonstrated that higher cTnT concentrations at admission are related with in-hospital mortality and elevated cTnT is an independent predictor of in-hospital mortality in acute ischemic right-sided stroke patients. We found no evidence for an association between cTnI and in-hospital mortality. We believe improved patient selection through biomarkers will prevent the possible cardiac disturbances due to impaired brain circulation.

References

1. Myers MG, Norris JW, Hachinski VC, Weingert ME, Sole MJ. Cardiac sequelae of acute stroke. *Stroke* 1982;13:838-42.
2. Cechetto DF, Hachinski V. Cardiovascular consequence of experimental stroke. *Baillieres Clin Neurol* 1997;6:297-308.
3. Brickner ME. Cardioembolic stroke. *Am J Med* 1996;100:465-74.
4. Apak I, Iltumur K, Tamam Y, Kaya N. Serum cardiac troponin T levels as an indicator of myocardial injury in ischemic and hemorrhagic stroke patients. *Tohoku J Exp Med* 2005;205:93-101.
5. 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.
6. 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;36:270-5.
7. Christenson RH, Duh SH, Newby LK, Ohman EM, Califf RM, Granger CB, et al. Cardiac troponin T and cardiac troponin I: relative values in short-term risk stratification of patients with acute coronary syndromes. GUSTO-IIa Investigators. *Clin Chem* 1998;44:494-501.
8. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Burvill PW, Anderson CS, et al. Five-year survival after first-ever stroke and related prognostic factors in the Perth Community Stroke Study. *Stroke* 2000;31:2080-6.
9. Wade DT, Langton Hewer R. Stroke: associations with age, sex, and side of weakness. *Arch Phys Med Rehabil* 1986;67:540-5.
10. Marklund N, Peltonen M, Nilsson TK, Olsson T. Low and high circulating cortisol levels predict mortality and cognitive dysfunction early after stroke. *J Intern Med* 2004;256:15-21.
11. Tamam Y, Iltumur K, Apak I. Assessment of acute phase proteins in acute ischemic stroke. *Tohoku J Exp Med* 2005;206:91-8.
12. Silvestri A, Vitale C, Ferretti F, Onorati D, Fini M, Rosano GM. Plasma levels of inflammatory C-reactive protein and interleukin-6 predict outcome in elderly patients with stroke. *J Am Geriatr Soc* 2004;52:1586-7.
13. Varona JF, Bermejo F, Guerra JM, Molina JA. Long-term prognosis of ischemic stroke in young adults. Study of 272 cases. *J Neurol* 2004;251:1507-14.
14. Bhatia RS, Garg RK, Gaur SP, Kar AM, Shukla R, Agarwal A, et al. Predictive value of routine hematological and biochemical parameters on 30-day fatality in acute stroke. *Neurol India* 2004;52:220-3.
15. Schlegel DJ, Tanne D, Demchuk AM, Levine SR, Kasner SE; Multicenter rt-PA Stroke Survey Group. Prediction of hospital disposition after thrombolysis for acute ischemic stroke using the National Institutes of Health Stroke Scale. *Arch Neurol* 2004;61:1061-4.
16. Heinsius T, Bogousslavsky J, Van Melle G. Large infarcts in the middle cerebral artery territory. Etiology and outcome patterns. *Neurology* 1998;50:341-50.
17. Haapaniemi E, Tatlisumak T, Soinne L, Syrjälä M, Kaste M. Natural anticoagulants (antithrombin III, protein C, and protein S) in patients with mild to moderate ischemic stroke. *Acta Neurol Scand* 2002;105:107-14.
18. Tokgözoglu SL, Batur MK, Top uoglu MA, Saribas O, Kes S, Oto A. Effects of stroke localization on cardiac autonomic balance and sudden death. *Stroke* 1999;30:1307-11.
19. Colivicchi F, Bassi A, Santini M, Caltagirone C. Cardiac autonomic derangement and arrhythmias in right-sided stroke with insular involvement. *Stroke* 2004;35:2094-8.
20. Critchley HD, Corfield DR, Chandler MP, Mathias CJ, Dolan RJ. Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. *J Physiol* 2000;523 Pt 1:259-70.
21. Oppenheimer SM, Hachinski VC. The cardiac consequences of stroke. *Neurol Clin* 1992;10:167-76.
22. 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(7248):1502-4.
23. 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;18:194-9.
24. Ay H, Arsava EM, Saribaş O . Creatine kinase-MB elevation after stroke is not cardiac in origin: comparison with troponin T levels. *Stroke* 2002;33:286-9.
25. Williamson JW, Nobrega AC, McColl R, Mathews D, Winchester P, Friberg L, et al. Activation of the insular cortex during dynamic exercise in humans. *J Physiol* 1997;503 (Pt 2):277-83.
26. Cheung RT, Hachinski VC, Cechetto DF. Cardiovascular response to stress after middle cerebral artery occlusion in rats. *Brain Res* 1997;747:181-8.
27. Demchuk AM, Felburg RA, Alexandrov AV. Clinical recovery from acute ischemic stroke after early reperfusion of the brain with intravenous thrombolysis. *N Engl J Med* 1999;340:894-5.