

# Creatine Kinase-MB Elevation After Stroke Is Not Cardiac in Origin

## Comparison With Troponin T Levels

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**Background and Purpose**—Creatine kinase-MB (CK-MB) increases in some patients with stroke, with no clear evidence of an acute coronary syndrome. Its elevations have been suggested to represent a biological marker for stroke-related myocardial injury. Troponin T has superior sensitivity and specificity to CK-MB in revealing minor myocardial injury. Therefore, we studied troponin T levels after stroke to determine whether troponin T increases in parallel to CK-MB.

**Methods**—We made daily measurements of CK-MB, myoglobin, total creatine kinase (total CK), and troponin T levels up to day 5 in 32 patients with large hemispheric infarction and with no history of coronary heart disease. The daily enzyme levels were compared with those of a control group of 22 patients with neurological diseases other than stroke.

**Results**—Serum CK-MB, myoglobin, and total CK levels were elevated above the cutoff value in 11, 26, and 20 patients with stroke, respectively. These enzyme levels gradually increased within the first 3 days and declined afterward. Troponin T did not exceed the reference range in any patients. One patient had elevated myoglobin and 3 had elevated total CK in the control group. The difference between groups was significant for CK-MB, myoglobin, and total CK at various time points.

**Conclusions**—Troponin T, a more specific biochemical marker of myocardial injury, does not increase after stroke. Normal troponin T along with elevated CK-MB signifies that CK-MB is not the biological marker for myocytolysis. CK-MB elevations in stroke patients are likely to be noncardiac in origin. (*Stroke*. 2002;33:286-289.)

**Key Words:** creatine kinase-MB ■ myocardial infarction ■ stroke, ischemic ■ troponin T

Creatine kinase-MB (CK-MB) activity has been shown to increase in certain patients with ischemic stroke, subarachnoid hemorrhage, and head trauma in the absence of any clinically evident acute coronary syndrome.<sup>1-4</sup> The temporal pattern of elevation was typically gradual and sustained for several days, unlike myocardial infarction, in which CK-MB peaks and falls within the first 24 hours of coronary artery occlusion.<sup>5</sup> A continuing low-grade myocardial necrosis suggestive of myocytolysis, the pathological hallmark of stroke-related cardiac damage distinguished by foci of swollen myocytes, interstitial bleeding, and mononuclear infiltration in the vicinity of cardiac nerves, has been implicated as the cause of CK-MB elevations.<sup>6</sup> However, CK-MB is not completely cardiac specific, also increasing in skeletal muscle disease or injury, kidney failure, intramuscular injection, strenuous exercise, and after exposure to several toxins and drugs.<sup>7-9</sup>

Troponin T is a 39-kDa polypeptide subunit of the myofibrillar regulatory troponin complex. Troponin T has several advantages over CK-MB<sup>7,10</sup>: (1) it is more cardiac specific; (2) its diagnostic efficiency for cardiac damage in victims of general body trauma or skeletal muscle injury is higher (94%,

as compared with 63% with CK-MB); (3) it persists longer in the circulation; (4) its proportional rise with respect to the discriminator value is higher, enabling the detection of trace amounts of damaged myocardium. A more sensitive, specific, and efficient marker for cardiac damage should perform better in reflecting the subtle cardiac changes occurring after stroke. Therefore, in the present study, we determined troponin T levels in a subset of patients with ischemic stroke in an attempt to demonstrate whether troponin T increases in parallel to CK-MB after stroke.

### Subjects and Methods

During an 18-month period, 32 patients with first-ever ischemic stroke, consecutively admitted within the first 24 hours of symptom onset, were included. Cerebral infarctions involved the cortical and subcortical regions in the territory of middle, anterior, or posterior cerebral arteries. Patients with hemorrhagic stroke and who had a history of angina pectoris or myocardial infarction were excluded. Those with signs of myocardial ischemia at admission were also excluded.

The daily serum levels of CK-MB mass, troponin T, total creatine kinase (total CK), and myoglobin were determined from the first to the fifth days. Venous blood was collected in tubes containing SST Gel and clot activator. The samples were centrifuged at 7000 rpm for

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**TABLE 1. Elevated Cardiac Enzyme Levels After Ischemic Stroke**

	CK-MB	Myoglobin	Total CK	Troponin-T
No. of patients with levels above reference range (n=32)	11	26	20	0
No. of measurements above reference range (n=109)	19	59	43	0
Dominant hemisphere infarction (No. of patients with elevated/normal levels)	6/10	12/4	10/6	0/16

10 minutes, and the serum was obtained within 1 hour of collection. Troponin T levels were determined by Elecsys Troponin-T, CK-MB mass by Elecsys CK-MB, myoglobin levels by Elecsys Myoglobin Short Turn Around Time Immunoassays, and total-CK by CK-NAC kit (Roche). The upper limits recommended by the manufacturer were 0.1 ng/mL, 5 ng/mL, 72 ng/mL, and 170 IU/L for troponin T, CK-MB, myoglobin, and total CK, respectively.

Twenty-two patients admitted for neurological diseases other than stroke were enrolled as the control group (5 with myasthenia gravis, 6 with peripheral neuropathy, 2 with Parkinson's disease, and 9 with multiple sclerosis). The same enzyme determinations were carried out in the control group on a single occasion. Enzyme levels between groups and among different time points were compared by use of the Mann-Whitney *U* test. A value of  $P < 0.05$  was considered significant. Spearman rank correlation coefficients were calculated to describe the association between variables.

## Results

The study group included 20 male and 12 female patients with a mean age of 62 years (range, 28 to 80 years). Twenty-four patients had infarction in the middle, 6 in the posterior, and 2 in the anterior cerebral artery territories. The control group consisted of 7 male and 15 female patients with a mean age of 45 years (range, 26 to 74 years). None of the patients had symptoms consistent with an acute coronary event at any time before the enzyme determinations were carried out. Overall, 109 samples from 32 patients were available for the enzyme measurements; blood samples at some time points, especially in patients with stroke onset at night, were missed. In all patients, there was at least 1 measurement performed within the first 2 days (Table 1).

CK-MB was elevated in 11 of the 32 patients (range, 5.15 to 21.74 ng/mL). There were 3 patients with levels between 7 and 10 ng/mL and 2 patients with levels  $> 10$  ng/mL (13.66 and 21.74 ng/mL). CK-MB values did not increase above the threshold in any patient in the control group. The difference between groups was significant on days 1, 2, 3, and 4 ( $P < 0.05$ ). Myoglobin was above the cutoff in 26 patients with stroke and in 1 patient without stroke (range, 72.28 to 1131.00 ng/mL); the difference between groups was statistically significant during the first 5 days (Table 2). All patients with high CK-MB values also had elevated myoglobin levels. Total CK was elevated above the reference in 20 patients with stroke and in 3 patients without stroke (range, 177.00 to 1754.00 IU/L). The difference between groups was significant on days 1, 2, 3, and 4. Similar to myoglobin, total CK was elevated in all patients with high CK-MB. Total CK, myoglobin, and CK-MB levels gradually increased within the first 3 days and declined afterward (Figure). However, for the each enzyme, the levels on subsequent days were not significantly different from the day-1 values. Unlike other enzymes, troponin T remained within the normal range in both

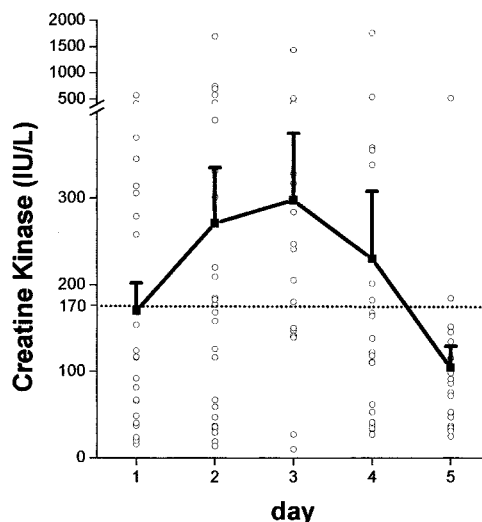
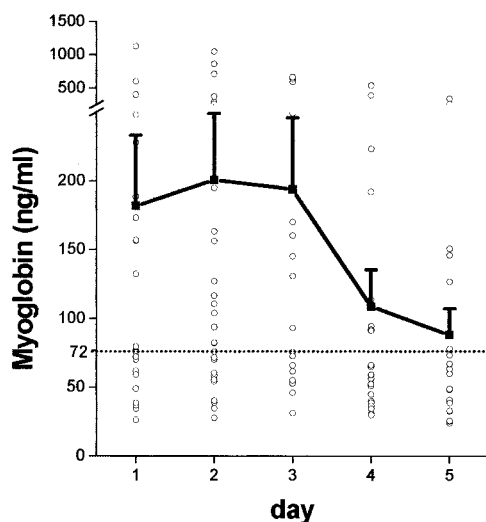
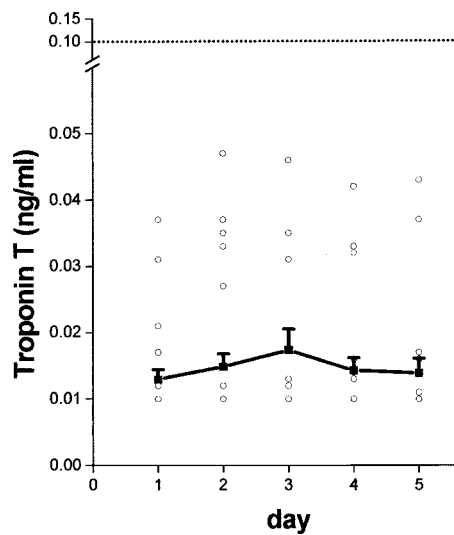
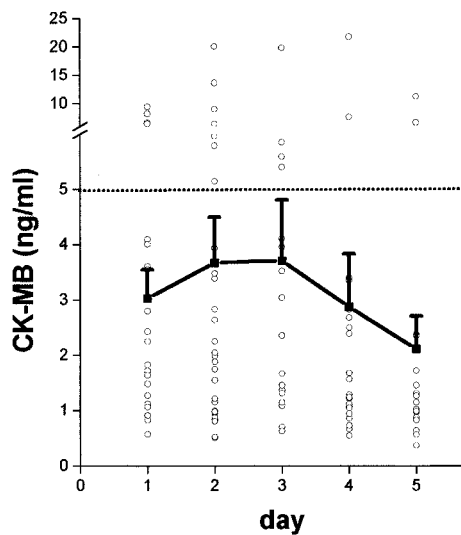
stroke and control patients (range, 0.010 to 0.047 ng/mL). Troponin T levels on days 2, 3, 4, and 5 did not differ from those of day 1, nor did they differ between groups at any time after stroke (Table 2).

CK-MB exhibited a temporal profile more similar to that of total CK ( $r = 0.675$ ,  $P < 0.05$ ) and myoglobin ( $r = 0.728$ ,  $P < 0.05$ ) than did troponin T ( $r = 0.147$ ,  $P = 0.128$  and  $r = 0.149$ ,  $P = 0.121$ , respectively). Total CK and myoglobin levels were correlated with each other during the first 5 days of stroke ( $r = 0.735$ ,  $P < 0.05$ ), whereas there was a weak correlation between troponin T and CK-MB levels during the same period ( $r = 0.200$ ,  $P < 0.05$ ).

## Discussion

Stroke-related myocardial injury is pathologically characterized by scattered foci of microlesions.<sup>11-13</sup> Troponin T increases above the cutoff value in clinical situations with trace amounts of injured myocardial tissue; it increases in 19% to 64% of patients with unstable angina pectoris, whereas CK-MB usually remains normal.<sup>8</sup> Likewise, troponin T but not CK-MB increases after endomyocardial biopsy, in which small amounts of tissue (12 to 14 mm<sup>3</sup>) are removed.<sup>14</sup> Given the superior discriminatory power of troponin T in minor cardiac injury, one might expect to see troponin T levels above the cutoff limit in stroke patients with suspected cardiac damage, based on CK-MB measurements. However, the present study of 32 patients with ischemic stroke showed that troponin T did not increase above the cutoff value, even in those with elevated CK-MB. Since a more sensitive marker for minor myocardial injury remains within the normal range, CK-MB elevations observed in patients with stroke do not reflect stroke-related myocardial cell necrosis.

In contrast to the previous studies that used CK-MB activity assay,<sup>1,3</sup> the current study is the first that has determined the temporal profile of CK-MB mass after stroke. CK-MB mass assay is more sensitive and specific than the activity assay for myocardial injury. CK-MB mass assay, in our cohort, revealed a gradual and sustained elevation similar to that observed in previous studies that used the activity assay.<sup>1,2,4</sup> Nevertheless, the origin of these CK-MB elevations in stroke patients remains to be elucidated. The finding of "normal troponin T along with elevated CK-MB" suggests that the rise in CK-MB is not of cardiac origin. In the present study, CK-MB correlated better than troponin T with the enzymes representing skeletal muscle turnover, total CK, and myoglobin. Patients with large hemispheric infarctions are subject to skeletal muscle injury caused by multiple injections. Moreover, negative caloric balance may occur in some because of inappropriate oral intake or fluid restriction with



Serum cardiac enzyme time courses in patients with ischemic stroke. Solid lines represent mean (error bars) serum cardiac enzyme levels. Horizontal dashed lines indicate upper limit of the reference range.

concern for brain edema. The latter limits the amount of intravenous or nasogastric calories leading to a starvation response with liberation of calories from the skeletal muscle.

**TABLE 2. Mean Daily Cardiac Enzyme Levels After Ischemic Stroke**

	CK-MB	Myoglobin	Total CK	Troponin T
Day 1 (n=23)	3.029*	181.616*	169.674*	0.013
Day 2 (n=28)	3.672*	200.473*	270.732*	0.015
Day 3 (n=17)	3.708*	193.520*	297.353*	0.017
Day 4 (n=22)	2.873*	108.470*	229.796*	0.014
Day 5 (n=19)	2.110	87.729*	103.974	0.014

Mean and median enzyme levels in the control group were 1.346 ng/mL and 0.76 ng/mL for CK-MB, 38.233 ng/mL and 32.590 ng/mL for myoglobin, 82.045 IU/L and 46.500 IU/L for total CK, and 0.012 ng/mL and 0.010 ng/mL for troponin T (ranges: 0.270 to 4.840 for CK-MB, 21.000 to 112.200 for myoglobin; 16.000 to 339.000 for total CK, and 0.010 to 0.030 for troponin T).

\*P 0.05 with respect to control.

Therefore, elevations in CK-MB might reflect a generalized lytic state, especially of the skeletal muscle.

In 2 of our patients with normal troponin T, CK-MB values exceeded the acute myocardial infarction threshold (10 ng/mL). False-positive results of CK-MB in patients with ischemic stroke may lead to a misdiagnosis of acute coronary syndromes. Indeed, coincidental acute coronary syndromes can occur in as much as 9% of patients with stroke during the hospitalization period.<sup>15</sup> The use of biochemical markers for the diagnosis of myocardial infarction is especially important in stroke patients, some of whom cannot fully communicate chest pain. In these patients, troponin T must be obtained, as it is not falsely elevated by the impact of stroke.

Troponin T, unlike other enzymes, remains elevated up to 2 weeks in the event of myocardial injury.<sup>7</sup> It is unlikely that any elevation in troponin T at the missing time points has escaped from our detection since enzyme levels were measured in all patients within the first 2 days, and there were at least 2 measurements performed on different days for each

patient. Normal troponin T after stroke suggests that its sensitivity for detecting myocytolysis is not sufficient. However, it should be noted that our cohort with large hemispheric infarctions and without coronary artery disease might represent a lower risk group for myocytolysis; including patients with smaller but strategically located infarctions for myocytolysis into our cohort, such as of the insular cortex,<sup>6</sup> might have caused more marked elevations in troponin T levels. Further studies with pathological verification are needed to establish an association between troponin T and myocytolysis. Such a study might set a lower cutoff value for myocytolysis than the customarily accepted limits for acute coronary events.

In conclusion, unlike CK-MB, troponin T does not increase after ischemic stroke. Therefore, elevated CK-MB levels do not translate into in vivo evidence of myocytolysis occurring after stroke. Especially important is the fact that CK-MB elevation in a stroke patient does not necessarily reflect an acute coronary event. Troponin T promises to be a valuable marker in this regard.

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