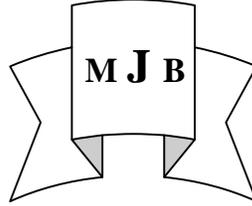


Prognostic Significance of Troponin T and Creatine Kinase-MB Activity in Sera of Acute Ischaemic Stroke Patients

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Abstract

Background and purpose: Elevation of sera cardiac troponin T (cTnT) concentration and creatine kinase-MB (CK-MB) activity and electrocardiographic changes can occur after ischaemic stroke. The aim of this study was to identify the relationships between elevated cardiac biochemical markers with ECG changes, stroke severity and in-hospital mortality and to look for source of CK-MB.

Patients and method: From 1 June 2009 to 1 October 2009 this study recruited 70 patients (46 males, 24 females) who were admitted to Merjan teaching hospital due to acute ischaemic stroke which confirmed by neurologist, blood samples were taken for cTnT and CK-MB measurement and ECG was done. The stroke severity as assessed by Scandinavian stroke scale, and in hospital death were compared between the two groups of the cTnT and CK-MB. Hypertension and diabetes were separately compared between two groups of cTnT and CK-MB.

Results: Sera cTnT concentration and CK-MB activity were elevated in 22.9%, 35.7% of cases respectively. ECG changes occurred in 45.7%. In contrast to elevated CK-MB activity, elevated cTnT associated with greater stroke severity and in hospital deaths. ECG changes were more in patients with elevated cTnT than in patients with elevated CK-MB. CK-MB was not elevated in most patients with elevated cTnT, the non parallel increase of CK-MB with cTnT signify the non cardiac source of CK-MB. Hypertension and diabetes mellitus were more common in the elevated cTnT patients than normal cTnT group.

Conclusion: Elevated sera cTnT in patients with acute ischaemic stroke were associated with severe neurological deficits and in hospital deaths. The elevated CK-MB was mostly non-cardiac source and not correlated with stroke severity and in hospital death. The elevated cTnT along with ECG changes, hypertension and diabetes mellitus signify underlying asymptomatic coronary artery disease.

الأهمية التكهنية لتروبونين تي وكرياتين كايبيز - ام بي في الطارئة الوعائية الدماغية الأقفارية الحادة

الخلاصة

الخلفية والغرض المُجرّد: ارتفاع المصل القلبي تروبونين تي [سي تي أن تي] وكرياتين كايبيز - ام بي [سي كي - أم بي] ورسم القلب الكهربائي [إي سي جي] تغييرات يُمكنُ أن تُحدُث بعد الطارئة الدماغية الاقفارية الحادة. هدف هذه الدراسة هو ان نوجد ١: العلاقات بين ارتفاع بروتينات العضله القلبية [سي تي أن تي، سي كي - أم بي] وبين تغييرات رسم القلب الكهربائي وشدة الطارئة وحالات الوفاة الناتجة إثناء الرقود في المستشفى، ٢: مصدر [سي كي - أم بي].

الطرائق: من ١/ يونيو/حزيران ٢٠٠٩ إلى ١/ أكتوبر/تشرين الأول ٢٠٠٩ شملت هذه الدراسة ٧٠ مريضاً متتالين أُدخلوا إلى مستشفى مرجان التعليمي بسبب الطارئة الدماغية الاقفارية الحادة، التي أُكِّدَت من قِبَل طبيب الأُصْغاب. خلال ٢٤-٣٦ ساعة بعد الدخول، تم اخذ عينات دم لقياس [سي تي أن تي] و[سي كي - أم بي] وأخذ رسم القلب الكهربائي. شدة الطارئة الدماغية الاقفارية الحادة كما هي مقيّمة من قبل مقياس الشدة الإسكندنافي [إس إس إس] وحالات الوفاة الناتجة إثناء الرقود في المستشفى قورنت بين مجموعتي ال [سي تي أن تي] و[سي كي - أم بي] كلا على حدا. تغييرات رسم القلب الكهربائي و ارتفاع ضغط الدم وداء السكري قورنت منفصلة بين مجموعتي [سي تي أن تي] و [سي كي - أم بي].

النتائج: ارتفع المصل [إسي تي أن تي و سي كي-أم بي] في [٢٢,٩%] و [٣٥,٧%] من الحالات على التوالي. تغييرات رسم القلب الكهربائي حدثت في [٤٥,٧%]. بالمقارنة مع ارتفاع [إسي كي-أم بي] ، ارتفاع [إسي تي أن تي] مرتبط بشدة الطارئه الدماغيه الاقفاريه الحادة الضربة وحالات الوفاة الناتجة إثناء الرقود في المستشفى. تغييرات رسم القلب الكهربائي كانت أكثر في المرضى المرتفع لديهم ال[إسي تي أن تي] من المرضى المرتفع لديهم ال[إسي كي-أم بي] . ال[إسي كي-أم بي] لم يرتفع لدى أكثر المرضى المرتفع لديهم ال[إسي تي أن تي] ، تبيّن من هذا عدم وجود الزيادة المتوازية لل [إسي كي-أم بي] مع الزيادة الحاصلة في ال [إسي تي أن تي] لذلك فإن مصدر ال[إسي كي-أم بي] بعد الطارئه الدماغيه الاقفاريه الحادة هو غير قلبي على الأرجح. ارتفاع ضغط الدم أو داء السكري كانا أكثر شيوعاً في المرضى المرتفع لديهم ال[إسي تي أن تي] .

الاستنتاج: مصل ال [إسي تي أن تي] المرتفع بعد الطارئه الدماغيه الاقفاريه الحادة أرتبط إحصائياً بشده الخلل العصبي وحالات الوفيات في المستشفى الناتجة عن الطارئه. مصدر ال[إسي كي-أم بي] بعد الطارئه الدماغيه الاقفاريه الحادة هو غير قلبي على الأرجح وليس مرتبطاً بشدة الطارئه وحالات الوفيات الناتجة في المستشفى. ال [إسي تي أن تي] المرتفع سوية مع ال[إسي كي-أم بي] المرتفع وتغييرات رسم القلب الكهربائي و ارتفاع ضغط الدم و داء السكري مؤشر قوي لمرض الشريان التاجي الغير ظاهر سريريا.

Introduction

The brain-heart connection was described early in the 20th century when Levy showed that changes in central nervous system (CNS) metabolism influenced cardiac function [1], In clinical practice, physicians regularly encounter patients with ECG changes related to CNS lesions .Repolarization disturbances and dysrhythmias occurring in acute stroke may be due to release of catecholamines into the patients general circulation [2], Direct neural effects mediated from the CNS via neurons ending on the heart [2], or coexisting ischaemic heart disease [3]. Whereas hormonal and neuronal effects on cardiac function at present are of uncertain clinical relevance, coexisting ischaemic heart disease represents a major issue. Although cardiac death after stroke is common, its incidence may not be entirely explained by concomitant coronary artery disease (CAD) [4], and as previous studies have demonstrated, brain injury alone may contribute directly to generation of cardiac dysfunction [5]. During the last decade, it has become evident that acute stroke in many cases is accompanied by a rise in the concentration of troponins in serum,

indicating concomitant coronary disease [6]. For the clinician, it is important to know whether ECG abnormalities encountered in stroke patients are caused by a coexisting acute coronary syndrome, as this would call for cardiologic intervention . Thus far, little is known about the clinical consequences of ECG and troponin changes in acute cerebrovascular disease.

Cardiac troponin are the most sensitive and specific markers for myocardial injury [7]. They enable the detection of trace amounts of damaged myocardium, even when creatine kinase-myocardial band (CK-MB) and ECG remains normal. Elevation in cardiac troponins may therefore be sensitive to subtle cardiac injury occurring secondary to cerebral infarction, provided that patients do not have concomitant coronary ischaemia.

There are discordant results of the possible role of cTnT in acute stroke[8]. Several mechanisms may be responsible for raised concentration of cardiac troponins during the early phase of stroke: primary myocardial damage with secondary cardioembolic cerebral ischaemia, primary cerebral ischaemia with secondary myocardial injury attributable to central activation

of sympathetic nervous system [9], or coexisting cardiac disease.

Creatine-kinase-MB (CK-MB) activity has been shown to increase in certain patients with ischaemic stroke, subarachnoid haemorrhage, and head trauma in the absence of any clinically evident acute coronary syndrome [10]. 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 [11].

Aim of Study

- 1) To identify myocardial markers [cTnT,CK-MB,ECG] in acute ischaemic stroke .
- 2) The relationship of elevated myocardial markers[cTnT,CK-MB,ECG] with stroke severity and in-hospital death.
- 3) To identify source of CK-MB.

Patients and Methods

From 1 June to 1 October of 2009, 85 patients were diagnosed as acute ischaemic stroke in the wards of Merjan teaching hospital . Inclusion was made as soon as the diagnosis of acute ischaemic stroke was confirmed by neurologist, acute ischaemic stroke was diagnosed according to history of focal neurological deficit for a few minutes to hours duration, general examination, neurological examination (focal neurological deficit finding), and brain CT scan.

By history and clinical examination 15 patients were excluded from the study, because they had matched the exclusion criteria. The exclusion criteria included any condition that might cause an increase in the serum cTnT level rather than stroke, which include the following:

- 1) Ischaemic heart disease
- 2) Heart failure

- 3) History of cardiac surgery and cardiac catheterization for non ischaemic cause within one month .

So 70 patients were included in this study, 12 leads ECG was recorded in all the patients at admission and on day one of hospital stay. The ECG registrations were interpreted by cardiologist, the ECG results dichotomized into normal and pathological findings. The definition of pathological findings according to the modified Minnesota code [12] which include:

- 1) ST segment depression (≥ 1 mm) in leads (I, II, aVL, aVF, V₁-V₆)
- 2) T wave inversion (≥ -5 mm) in leads (I, II, V₂- V₆)
- 3) AV conduction (PR > 0.21 s) in leads (I, II, III), partial AV-block and complete AV-block
- 4) Ventricular conduction, (QRS > 0.12 s)
- 5) Atrial fibrillation.

In addition to the standard blood samples, venous samples for cTnT and CK-MB were analyzed in all patients on day one (after 12-24 hours of admission). For statistical analysis , cTnT results were dichotomized into normal (≤ 0.035 ng/ml), or high (>0.035 ng/ml, CK-MB results were dichotomized also into normal (≤ 25 IU/L), and high (> 25 IU/L), regarding cTnT cut-off level , the European society of cardiology and American college of cardiology recommends using 0.035 ng/ml as cTnT cutoff value for diagnosis of cardiac injury[13] . This value refers to 99th percentile of a reference population with a coefficient of variation of < 10% . In this study the troponin T was assessed by Biomeruex (France) kit with the aid of Minividus assay, while CK-MB had been

assessed by Biolab (France) kit using Kinetic method (SpecteroPhotoMeter). Another data from the patients' records regarding hypertension, diabetes mellitus and smoking were recorded. Hypertension ($\geq 140/85$ or known case of HPT) and diabetes mellitus (fasting blood sugar ≥ 126 mg/dl ,

random blood sugar >200 mg/dl , or known case of DM) .

Stroke severity was assessed by The Scandinavian Stroke Scale (SSS), {score ranged from 2 to 56 and patients were divided in to score of >20 , and score ≤ 20 }.

In-hospital outcome was divided into {Survival and Death} .

The Scandinavian Stroke Scale:

Function	Score
1. Consciousness	
• Fully conscious	6
• Somnolent, can awake to full consciousness	4
• React to verbal command, but not fully conscious	2
2. Eye movement.	
• No gaze palsy	4
• Gaze palsy present	2
• Conjugate eye deviation	0
3. Arm motor power	
• Raise arm with normal strength	6
• Raise arm with reduced strength	5
• Raise arm with flexion in elbow	4
• Can move but not against gravity	2
• paralysis	0
4. Hand motor power	
• Normal strength	6
• Reduced strength in full range	4
• Some movement, finger tips don't reach palm	2
• Paralysis	0
5. Leg, motor power	
• Normal strength	6

<ul style="list-style-type: none"> • Raises straight leg with reduced strength • Raises leg with flexion of knee • Can move, but not against gravity • Paralysis 	<p>5</p> <p>4</p> <p>2</p> <p>0</p>
<p>6. Orientation</p> <ul style="list-style-type: none"> • Correct for time, place and person • Two of these • One of these • Completely disoriented 	<p>6</p> <p>4</p> <p>2</p> <p>0</p>
<p>7. Speech</p> <ul style="list-style-type: none"> • No aphasia • Limited vocabulary or incoherent speech • More than Yes/No, but no larger sentences • Only Yes/No 	<p>10</p> <p>6</p> <p>3</p> <p>0</p>
<p>8. Facial palsy</p> <ul style="list-style-type: none"> • None dubious • Present 	<p>2</p> <p>0</p>
<p>9. Gait</p> <ul style="list-style-type: none"> • Walk 5 meters without aids • Walks with aids • Walks with help of another person • Sits without support • Bed ridden/ wheel chair 	<p>12</p> <p>9</p> <p>6</p> <p>3</p> <p>0</p>
<p>* The maximum score is 56, and the minimum is 2.</p> <p>* The motor power assessed only on the affected side</p>	

Statistical analysis

Correlation between variables assessed by chi square , P value <0.05 was considered significant . SPSS version

15 was used to calculate statistical analysis.

Results

A total of 70 patients with acute ischaemic stroke were enrolled in this study , 46 (65.7%) were males and 24 (34.3%) were females with mean age of 60 ± 8.2 years (ranging from 35 to 85 years) and mean duration of the patients stay in hospital was 4 days (ranging from 3 to 7 days) .

According to level of cTnT patients were divided in to two groups , group with elevated cTnT included 16 patients (22.9%) and group with normal cTnT included 54 patients (77.1%) .

According to level of CK-MB the patients also divided into two groups , group with elevated CK-MB included 25 patients (35.7%)and group with normal CK-MB included 45 patients (64.3%) .

ECG abnormalities based on modified code of Minnesota were found in 32 patients (45.7%) .

According to Scandinavian stroke scale 48 patients (68.6%) found to have score > 20 while 22 patients (31.4%) got score ≤20 .

Hypertension was found in 33 patients (47.1%) while diabetes mellitus was found in 13 patients (18.6%) .

In hospital death occurred in 6 patients (8.6%) .

The clinical characteristics of patients groups according to level of cTnT showed significant relationship between increase level of cTnT with hypertension and diabetes as shown in the following table.

Table I The clinical characteristics of patients groups according to level of cTnT

Variable	Elevated cTnT N.16	Normal cTnT N.54	P value
Age	61 ± 9.3	60 ± 7.4	0.6594
Male	10 (62.5%)	36(66.6%)	0.7578
Hypertension	13 (81.2%)	20 (37%)	0.0019
Diabetes mellitus	11 (68.7%)	2 (3.7%)	0.00001
Smoking	10 (62.5%)	23(42.6%)	0.1612

The clinical characteristics of the patients groups according to level of CK-MB showed no statistical

difference as shown in the following table .

Table II Clinical characteristics of patients groups according to level of CK-MB .

Variable	Elevated CK-MB N.25	Normal CK-B N.45	P value
Age	59 ± 8.5	60 ± 7	0.5989
Male	15 (60%)	31(68.9%)	0.4528
Hypertension	10 (40%)	23 (51.1%)	0.3722
Diabetes mellitus	5 (20%)	8 (17.8%)	0.8188
Smoking	12 (48%)	21(46.7%)	0.9147

In comparison of ECG changes , stroke severity based on Scandinavian stroke scale (SSS) and in – hospital death among patients with elevated and

normal serum cTnT , there was statistically significant correlation as shown in the following table .

Table III Results of ECG changes , stroke severity and in hospital death in patients with elevated and normal CTnT

Variable	Elevated cTnT N.16	Normal cTnT N.54	P value
ECG abnormalities	14 (87.5%)	18 (33.3%)	0.0001
SSS≤ 20	11(68.8%)	11(20.4%)	0.0002
Death	4 (25%)	2(3.7%)	0.0075

In comparison of ECG changes , stroke severity and in hospital death between patients with elevated and normal CK

- MB , there was no statistically significant correlation as shown in the following table .

Table IV Results of ECG changes , stroke severity and in hospital death between patients with elevated and normal CK. MB

Variable	Elevated CK-MB N.25	Normal CK-MB N.45	P value
E CG abnormalities	12 (48%)	20 (44.4%)	0.7748
SSS≤ 20	8(32%)	14(31.1%)	0.9388
Death	1 (4%)	5(11.1%)	0.3085

It was found that there was no relationship between the patients whom they got elevation in cTnT and those who got elevation in CK – MB (not the same patients) . Out of 16 patients with elevated cTnT there was 9 patients with normal CK - MB and 7 patients with elevated CK-MB and out of 54 patients with normal cTnT there was 36 patients with normal CK-MB and 18 patients with elevated CK-MB .

Discussion

The study suggested that the changes in cardiac biochemical markers and ECG changes in acute ischaemic stroke can predict in-hospital outcome [14] .

In this study the occurrence of ECG changes in acute ischemic stroke can be explained by 1} neural cause and 2} cardiac cause [15,16] . The neural cause was attributed , according to previous and current studies[2,16] , to increase intracranial pressure and

affection of insular region in the brain resulting in abnormal autonomic function and catecholamine discharge. This ECG changes tend to be rhythm and conductive abnormality[6,17] , while the cardiac causes of ECG changes ,which explain the significant correlation between elevated cTnT and ECG changes, in acute ischaemic stroke are caused by myocardial injury which is due to stress exerted by increase discharge of catecholamine and concomitant asymptomatic cardiac disease {mostly coronary artery disease}which also due to stress exerted by acute stroke and resulting acute coronary syndrome . In contrast to neural cause ECG changes , the cardiac causes of ECG changes tend to be ischaemic-like ECG changes [6,15,18] .

Despite there are few studies [19,20]that support the association between elevated cTnT and stroke severity ,in this study significant

relationship [P value <0.05] was found .

Also this study showed a statistically significant correlation [P value <0.05] between elevated cTnT and in-hospital deaths, a raised serum concentration of cTnT among patients with acute ischaemic stroke is related to increase in mortality supported by other studies {p value<0.05} [5,21,22]. This can be explained by the fact that every cerebrovascular accident is likely to exert considerable stress on the patients hearts[22,23,24] . Patients with underlying asymptomatic cardiac disease , specially coronary artery disease , probably have a reduce prestroke cardiac function . Elevated cTnT , therefore , may represent a lower cardiac tolerance to stress caused by cerebrovascular events[20,22,24] . This may be important explanation for the relationship between elevated cTnT and in-hospital deaths present in this study and as have been shown in other studies [P value <0.05] [20,21,22,25].

The statistically significant relationship [P value <0.05] between elevated cTnT with hypertension and diabetes [26] can be explained by high prevalence of underlying coronary artery disease in patients with diabetes or hypertension , and as mentioned above , the underlying diseased hearts unable to tolerate the stressful condition in the acute ischaemic stroke .

CTnT increases above the cutoff value [0.035ng/ml] with trace amounts of injured myocardial tissue. ,it increases in 19% to 64% of patients with unstable angina pectoris , whereas CK-MB usually remain normal . Likewise , cTnT but not CK-MB increases after endomyocardial biopsy , in which small amount of tissue {12-14mm³} are removed[27] . Given the superior discriminatory power of cTnT in minor cardiac injury , one might expect to see cTnT level above cutoff

limit in stroke patients with suspected cardiac damage [24,28] .

In the present study patients with acute ischaemic stroke showed that cTnT didn't increase above the cutoff (0.035ng/ml) in most CK-MB positive patients. So elevated CK-MB observed in patients with stroke don't reflect stroke-related myocardial cells necrosis , the origin of these CK-MB elevations remain to be elucidate , the finding of normal cTnT along with elevated CK-MB suggests that the rise in CK-MB is most likely non cardiac origin[24,28,29] . The possible explanations of these CK-MB elevations are skeletal muscles injury caused by multiple injections , negative caloric balance[30] and may be cardiac source when the elevation reaches the myocardial ischaemic levels and in parallel with elevated cTnT [29] . Given the most likely non cardiac source of CK-MB and as mentioned above , it poorly correlate with stroke severity and in-hospital death [P value >0.05].

While our study found a relationship between elevated cTnT and short-term prognosis in acute ischaemic stroke ,some studies do not suggest that[31,32] Several explanations for the difference between results of studies dealing with short-term and long-term outcome after stroke are plausible . The effect of acute stroke may be different from these of chronic state , possibly due to reorganization of neuronal circuitry and balancing between parasympathetic and sympathetic nervous system activity[33] .

Conclusion

1)Serum cTnT elevation correlates with stroke severity and in-hospital deaths and along with ischaemic-like ECG changes in DM or HPT patients may signify the underlying asymptomatic coronary artery disease

which warrant more evaluation and treatment for cTnT positive patients .
2) Elevated CK-MB were most likely non cardiac origin and not correlate with stroke severity and in-hospital deaths .

Recommendations

- 1) It is important to routinely measure serum cTnT in patient with acute stroke
- 2) The cTnT positive patient warrant further evaluation to exclude underlying asymptomatic CAD.

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