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Discordant Cardiac Troponin Results in Amphetamine – Related Rhabdomyolysis

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Abstract : **A case of a patient who developed amphetamine-related rhabdomyolysis and acute renal failure after an intestinal operation is reported. He initially had biochemical evidence of myocardial injury, with a concomitant increase in cardiac marker proteins CK-MB, cardiac troponin T (cTnT) and cardiac troponin I (cTnI) during the acute event. Following intensive treatment and improvement in renal function, levels of all myocardial marker proteins fell towards the normal range. Late in the course of the disease, however, there were re-elevations of CK-MB and cTnT, but not of cTnI, to levels exceeding 14 fold and 8 fold the upper limit of the reference range, respectively. Since, at present the possibility of re-expression of both CK-MB and cTnT in damaged and regenerating skeletal muscle can not be ruled out, the late occurrence of increased CK-MB and cTnT in our patient should not be interpreted as evidence of recurrent myocardial injury.**

Key words : Troponin T, Troponin I, amphetamine, rhabdomyolysis.

เรื่องย่อ : ผลของ Cardiac Troponins ที่ขัดแย้งกันในผู้ป่วยที่เสพย์ยา Amphetamine และเกิดภาวะกล้ามเนื้อลายสลาย

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คณะผู้รายงาน ได้นำเสนอผู้ป่วยชาย 1 ราย ที่มีประวัติเสพย์ยา amphetamine และเกิดปัญหากล้ามเนื้อลายสลายและไตวายเฉียบพลันภายหลังจากได้การรับการผ่าตัดช่องท้อง ผลการตรวจทางห้องปฏิบัติการในระยะแรกพบหลักฐานของการมี injury ของกล้ามเนื้อหัวใจ โดยพบว่ามีการเพิ่มขึ้นของระดับ CK-MB, cardiac troponin T (cTnT) และ cardiac troponin I (cTnI) ในเลือด ภายหลังจากที่ผู้ป่วยได้รับการรักษาและภาวะการทำงานของไตดีขึ้น พบว่าระดับของสารเหล่านี้ลดลงมาอยู่ในเกณฑ์ปกติ อย่างไรก็ตาม ในสัปดาห์ที่ 2 หลังการผ่าตัด พบว่ามีการเพิ่มสูงขึ้นใหม่อีกครั้งของ CK-MB ถึง 14 เท่าค่าสูงสุดของค่าปกติ และ cTnT ขึ้นเป็น 8 เท่าค่าสูงสุดของค่าปกติ แต่ระดับ cTnI ไม่สูงขึ้น การสูงขึ้นของ CK-MB และ cTnT ในครั้งนี้ อาจเกิดเนื่องจากเกิดการ re-expression ของกล้ามเนื้อลายในช่วง regeneration ดังนั้นการแปลผลสำหรับการสูงขึ้นของโปรตีนทั้งสองในระยะท้ายนี้จึงไม่ควรคิดว่าเกิดจากภาวะการทำลายของเซลล์กล้ามเนื้อหัวใจ

INTRODUCTION

Measurement of cardiac troponin concentrations have become the standard biochemical method for diagnosis of myocardial infarction (MI) and detection of myocardial cell damage in a variety of clinical conditions associated with cardiac myocyte injury.[1,2] The monoclonal antibodies used in the immunoassay system for determining cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are highly specific for cardiac troponin molecules and show no cross-reactivity with the corresponding skeletal muscle troponin isoforms.[3] In acute coronary syndromes (unstable angina pectoris, non-Q-wave and Q-wave MI) a parallel increase in cTnT and cTnI levels is usually observed in most patients.[4,5] There are, however, several clinical conditions in which the troponins show discordant results.[6-8] We report here a case of patient with amphetamine-related rhabdomyolysis who exhibited a significant increase in cTnT but not in cTnI concentration during the course of the disease.

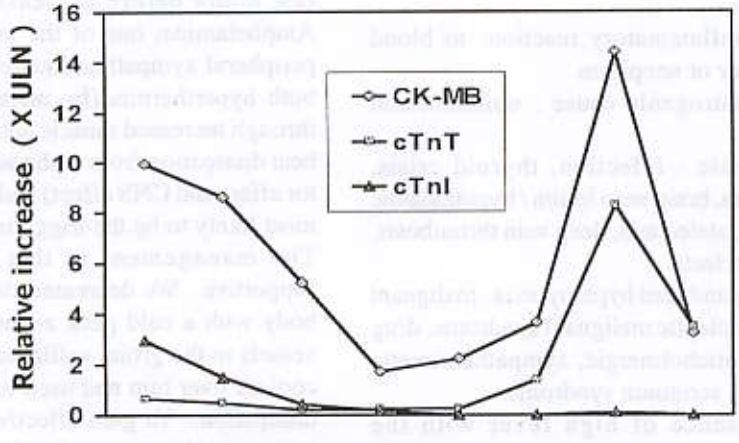
CASE REPORT

A 27-year-old man presented to the emergency unit with a complaint of crampy abdominal pain diffusely distributed over the pubic region with radiation to the scrotum on both sides that was not accompanied by nausea or vomiting. There was no history of injury in the past few days but he later admitted to take amphetamine regularly. At the time of presentation, the patient was agitated. His blood pressure was 150/100 mmHg; he had a sinus tachycardia (128 beats per minute) and his respiratory rate and core temperature were 20 per minute and 37.3°C, respectively. On physical examination, the abdomen was distended, with tenderness and guarding over the pubic region and rigidity around the umbilical area. Because of these findings, an exploratory laparotomy was performed which revealed situs inversus of the internal organs with dark coloration and a foul odour from the distal part of the ileum and the sigmoid colon. A diagnosis of internal herniation with bowel gangrene was made and a sigmoidectomy (Hartman procedure) as well as resection of the distal jejunum and proximal ileum with end-to-end jejunoileostomy was performed.

On the first day after operation he developed a high fever and respiratory alkalosis. His temperature, which was 38°C before operation, rose to a maximum level of 41.2°C after the first operative day. At that time the patient became confused and developed tachycardia and tachypnea (40 breaths/min). Blood gases showed a respiratory alkalosis with mild oxygenation disturbance (ABG : pH 7.5, PaO_2 229 in FiO_2 = 0.6, $PaCO_2$ 21, HCO_3 18, O_2sat 99%). Because of this severe hypermetabolic disorder, the patient was intubated and transferred to the ICU. During this critical period there was a transient drop in blood pressure. Poor peripheral perfusion with a low and dark brown urine output was observed. Initial screening tests showed evidence of rhabdomyolysis, with a serum creatine kinase (CK) activity of 21,010 U/L. Urine testing for

myoglobin was positive and there was an increased serum creatinine level (3.3 mg/dl). Because of the history of amphetamine abuse and a positive result for the presence of amphetamine in urine, an electrocardiographic assessment of cardiac involvement was performed which showed a sinus tachycardia (150 beats per minute). Measurement of the cardiac-specific protein troponin T (Elecsys 2010, Roche Diagnostics; upper limit of normal (ULN) = 0.10 ng/ml) showed a concentration of 0.354 ng/ml, which is indicative of minor myocardial injury. Since levels of cTnT have repeatedly been reported to be elevated in a significant proportion of patients with renal failure who had no evidence of cardiac damage, determination of cardiac troponin I (Vitros ECI, Ortho Clinical Diagnostics; ULN = 0.10 ng/ml) was performed the next day which also showed an increased level of 0.297 ng/ml.

Figure 1 demonstrates the results of serial measurements of cardiac marker proteins obtained over several weeks in the postoperative peroid. There was a gradual decline in the levels of total CK and CK-MB mass (Elecsys 2010; ULN = 5.0 ng/ml) as well as of the troponins to the corresponding reference range. However, both CK-MB and cTnT concentrations began to rise again 9 days after the operation, reaching a maximum level on the 18th post-operative day of 72 ng/ml (14 fold the ULN) and of 0.83 ng/ml (8 fold the ULN), respectively. Determinations of both markers on the day of discharge (27th post-operative day) revealed that levels of CK-MB and cTnT were still above the reference range. During the post-operative period, no significant increase in cTnI serum concentrations was observed and the patient never complained of chest pain.



CK	136,000	459,400	416,800	215,400	29,800	5,735	749	136
CK-MB (%)	0.04	0.01	0.01	0.00	0.04	0.32	9.6	11.9
Creatinine	1.2	0.8	0.5	0.4	0.4	0.5	0.7	0.8

Figure 1. Pattern of CK-MB mass, cTnT and cTnI release following rhabdomyolysis. The corresponding values of CK (U/L), CK: CK-MB ratio and creatinine (mg/dl) are demonstrated below the curve.

DISCUSSION

Etiologic factors and management in rhabdomyolysis

Rhabdomyolysis is a clinical condition in which injury to skeletal muscle results in leakage of the cellular content into the blood and, in the most severe form, passage of a large amount of myoglobin into the urine causing renal failure. The causes of rhabdomyolysis are many and include the following: direct physical injury (crush syndrome, burns), excessive muscular activity (seizures, military training), infection (bacterial or viral), inflammatory myopathies (polymyositis, dermatomyositis), metabolic disorders (diabetic ketoacidosis, hypokalaemia), extreme temperature (hyper/hypothermia) and drugs (alcohol, cocaine, amphetamines).[9]

The mechanism of post-operative hyperthermia as was seen in our patient is either an increase in heat production, a decrease in heat dissipation or disruption to the thermostat function of the hypothalamus[10,11] that can be encountered in many conditions such as

- An inflammatory reaction to blood transfusion, surgery or neoplasm
- An iatrogenic cause : unintentional over - heating
- Disease : infection, thyroid crisis, pheochromocytoma, brain stem lesion / hypothalamic injury or bleeding, atelectasis, deep vein thrombosis, osteogenesis imperfecta
- Drug-induced hyperpyrexia : malignant hyperpyrexia, neuroleptic malignant syndrome, drug poisoning from anticholinergic, sympathomimetic or stimulant drugs, serotonin syndrome.

The presence of high fever with the development of rhabdomyolysis pointed to drug-induced hyperpyrexia as the etiologic factor in the differential diagnosis of our patient. He was unlikely to have malignant hyperpyrexia (MH), a genetic disorder of the gene encoding the skeletal muscle sarcoplasmic reticulum Ca++ release channel, even though he had received succinyl choline and isoflurane during anaesthesia which may trigger MH in those with the disorder. However, the patient had no family history of MH, and the pattern of fever did not show an early progressive increase following the administration of triggering agents as is normally seen in MH during the operation[12,13] or only few hours after operation but this patient had peak fever at 33rd hour postoperative. Furthermore, he had no signs suggestive of contracture or rigidity of skeletal muscle and no respiratory acidosis as a result of severe hypermetabolism. By grading the score for malignant hyperpyrexia[14] for rigidity, muscle breakdown, respiratory acidosis, temperature, cardiac involvement, familial history and others, we found that he had a raw score of 28 or MH rank = 4. This mean that the likelihood of having an MH is borderline (greater than likely) but not very likely. Although the patient had 2 major (fever, elevated CK activity) and 4 minor criteria (tachycardia, tachypnea, altered conciousness and abnormally high blood pressure) of the neuroleptic malignant syndrome,[15] this condition is unlikely to be the cause of rhabdomy-olysis as he had no history of taking drugs known to induce this syndrome.

Our patient had a previous history of chronic amphetamine abuse and this drug had been taken a few hours before presentation to the hospital. Amphetamine, one of the most potent central and peripheral sympathomimetic amines,[16,17] can cause both hyperthermia (by increasing heat production through increased muscle activity and by decreasing heat dissipation from alpha adrenergic vasoconstrictor effect and CNS effect) and rhabdomyolysis and is most likely to be the triggering agent in our patient. The management in this patient was mainly supportive. We decreased the fever by cooling the body with a cold pack at the sides of major blood vessels in the groin, axilla, and neck, and also blew cool air over him and used turbid sponging for heat dissipation. To gain effective heat dissipation and to prevent shivering and reflect vasoconstriction, the patient was paralyzed with a nondepolarizing muscle relaxant (atracurium). The acute renal failure caused by rhabdomyolysis was treated by alkalinizing the urine and aggressive hydration (1/2 NSS 1,000 ml + $NaHCO_3$ 50 ml i.v. drip according to CVP and urine volume to 200 ml/hr).[18] Even though sodium bicarbonate is still controversial in the treatment of amphetamine-induced rhabdomyolysis because alkalinized urine might delay amphetamine excretion, it was decided to give sodium bicarbonate together with the fluid for the induction of diuresis

in order to alkalinize the urine because of a progressive rise in CK (highest level > 400,000 U/L). The reason was that although at the time the patient was admitted to the ICU it was more than 24 hours after taking the drug so that only a small amount of amphetamine should be left in his body, there might have been an ongoing effect of the drug in inducing muscle injury and rhabdomyolysis causing further injury to the tubular cells. After intensive treatment, the patient began to improve clinically and was extubated on the 5th day after ICU admission. He was sent back to the ward on the 9th day after the operation.

Myocardial ischemia in amphetamine abuse

The recreational drugs – cocaine, amphetamine, methamphetamine – have been reported to have adverse effects on the cardiovascular system. These compounds act by inhibiting norepinephrine reuptake at the peripheral sympathetic nerve terminal as well as by stimulating central sympathetic outflow. The sympathetic activity leads to varying degrees of tachycardia and systemic vasoconstriction.[19] Over the past decade, many reports have documented cocaine-related myocardial ischemia and infarction (for review see Lange and Hillis[20]). However, myocardial ischemic events related to amphetamine abuse have rarely been reported in the literature.[21,22] It has been postulated that amphetamine abuse, similar to that of cocaine, may cause systemic and coronary vasospasm that results in a decrease in myocardial blood flow and, in severe cases, platelet aggregation with subsequent thrombosis and infarction.[23,24] In the present case, although there was no evidence of ischemic myocardial injury on electrocardiogram, the findings of slight but significant increases both in cTnT and cTnI levels in the few days following operation and a subsequent decline thereafter are indicative of minor myocardial injury. In this context, it should be noted that although the isoenzyme CK-MB is normally found in only a small quantity in skeletal muscle, it can be released into the circulation in a considerable amount in patients with massive skeletal muscle damage.[25] Thus, measurement of CK-MB is an unreliable method for assessing the degree of myocardial damage in our patient.

Possible explaination for discordant cardiac troponins results

The main finding in this patient who developed amphetamine- related rhabdomyolysis after an intestinal operation, was a significant increase in the cardiac marker proteins CK-MB and cardiac troponin T (cTnT) without a concomitant elevation of cardiac troponin I (cTnI) late but not in the early course of the disease in a patient without classical signs of myocardial necrosis. The question thus arises, as to whether the discrepant results observed reflect a false-negative result of cTnI assay or false-positive results for CK-MB and cTnT determination.

Previous studies have shown that in patients with chronic renal failure who had no apparant signs and symptoms of ischemic myocardial injury, an increase in serum concentration of cTnT is frequently observed and the frequency of increased cTnT (18-75%). was much higher than that of cTnI (4-17%).[3,8] The reasons for these differences is not known at present and studies performed with reverse transcription polymerase chain reaction (RT-PCR) and western blot analysis of biopsy specimens of skeletal muscle have yielded conflicting results.

In developing fetal skeletal muscle, several isoforms of cTnT are present but are down-regulated after birth. A similar mechanism also exists for the B-subunit of CK. In contrast, cTnI is not expressed during any stage of skeletal muscle development.[26] The developmental changes in cTnT have led to the assumption that, similar to CK-MB, there might be re-expression of cTnT in damaged or regenerating skeletal muscle. By using western blot analysis, Mc Laurin, et al.[27] first reported expresssion of cTnT, but not cTnI, in skeletal muscle biopsies of chronic dialysis patients without acute ischemic heart disease. Their results were confirmed by a study of Richiuti and Apple[28], but not by that of Haller, et al.[29], who showed no evidence of expression of either cTnT mRNA or protein in truncal skeletal muscle biopsies of patients with end-stage renal disease (ESRD). Recently, Fredericks, et al.[30] reported that only minute quantities of cTnT were detected by immunoblotting or immunhistochemistry in exterior oblique muscle samples from patients with ESRD.

With regard to acute renal failure, several trials using the second-generation or third-generation cTnT assay have reported no increase in cTnT serum concentration in patients with rhabdomyolysis.[3,31] However, all of these studies were performed on patients in the early stage of the disease, when the enzyme CK and myoglobin had reached their maximum values. In contrast, the re-elevation of both CK-MB and cTnT but not of cTnI concentration found in our patient occured late in the course of the disease, when the levels of CK fell to the normal range. In this case, a false-negative cTnI result is not likely for 2 reasons. Firstly, there was a concordant elevation of all marker proteins in the early phase of rhabdomyolysis. Secondly, the picture of a delayed increase in CK-MB and cTnT concentrations and the prolonged elevation of CK-MB late in the course of the disease are not typical of ischemic myocardial injury. Recently, Isotalo et al.[32] described a patient with metastatic alveolar rhabdomyosarcoma who had a sustained increase in CK-MB and cTnT levels but a normal cTnI concentration during the course of the disease. They theorized that rhabdomyosarcoma anaplasia leads to an immature skeletal muscle phenotype causing false-positive cardiac marker testing secondary to expression of CK-MB and cTnT. Thus, our hypothesis is that, there might also be a transient re-expression of the cTnT isoform that is released into the circulation in regenerating skeletal muscle of patients with rhabdomyolysis.

CONCLUSION

Discordant cardiac troponins results, with an increase in cTnT but not in cTnI concentration, are not uncommon in clinical laboratory practice and may be found in a significant proportion of patients with renal failure who have no evidence of cardiac involvement. Because the possibility of re-expression of cTnT in uremia and regenerating skeletal muscle can at present not be ruled out, the presence of elevated cTnT serum concentration in these patients should be interpreted with caution as evidence of myocardial injury. In such a case, determination of cTnI may be a more cardiac-specific method for detection of myocardial ischemia and infarction.

Comment

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The introduction in the early 1990's of sophisticated immunoassay systems for determining cardiac troponin T (cTnT) and troponin I (cTnI) has led to a revolution in the technology for cardiac marker measurement. The advantage of these marker proteins lies in their ability to provide a sensitive and specific diagnosis and prognostic risk assessment as well as to guide therapy in patients with acute coronary syndromes. There are, however, several important limitations of troponin measurement that need to be considered. Since the troponins can be detected in the circulation only 4 hours after the onset of ischemic symptoms and because of their prolonged time of elevation, they are not useful as early markers of myocardial necrosis and for the diagnosis of recurrent infarction. Another limitation of cardiac troponins lies in the fact that a significant number of patients with inflammatory myopathies (polymyositis/dermatomyositis), muscular dystrophy and chronic renal failure without clinical evidence of cardiac involvement show increased concentrations of the troponins, especially of cTnT. The report in the present study of increased cTnT and not cTnI levels late in the course of rhabdomyolysis adds to the findings mentioned above. However, in the light of a possible cTnT re-expression in regenerating skeletal muscle, the finding of an increase in cTnT serum concentration in patients with destructive skeletal myopathies should be interpreted cautiously. Nevertheless, the results of this report deserve confirmation from future investigations.

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