ELEVATED CK-MB WITHOUT MYOCARDIAL INFARCTION

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Introduction

Multiple etiological factors have to be considered when faced with isolated elevation of Creatine Kinase-MB (CK-MB), an isoenzyme of Creatine Kinase (CK) without any change in total CK or increase in Troponin. These factors must be kept in mind before diagnosing a patient with acute coronary syndrome (ACS) and subjecting them to further investigation and therapy which could involve anticoagulation, exposing patients to risk of bleeding and invasive procedures which have their own inherent risk. We present a case of a patient with atypical chest pain who was found to have elevated CK-MB but with normal total CK and Troponin levels.

Case Report

A 67 year old gentleman with past medical history of aortic stenosis status post porcine valve replacement, chronic obstructive lung disease, congestive heart failure and mitral regurgitation, was presented to the emergency room with complaints of a typical chest pain. The chest pain had lasted for about two hours, was non-exertional and non-radiating in nature. He had no associated sweating, dizziness, shortness of breath or nausea. His electrocardiogram demonstrated old left bundle branch block. In the emergency room, his serum Troponin was found to be less than 0.01 ng/ml and total CK of 32 Units/L. But his CK-MB fraction was elevated at 11.5 Units/L, which was 36% of the total CK. . He was admitted for further evaluation and to rule out myocardial infarction. Two more sets of cardiac enzyme analysis at six hour intervals showed normal Troponin and total CK, but continued elevation of CK-MB fraction at 10.5 and 10.6 Units/L. An echocardiogram showed normal left ventricular size, severe concentric left ventricular hypertrophy, impaired relaxation of left ventricle and ejection fraction of 50-55 % with normal wall motion. The prosthetic aortic valve was well seated and appeared to be functioning normally. He was admitted for a similar complaint four months back. During that admission it was also noted that the patient had normal troponin and normal total CK levels, but elevated CK-MB levels ranging between 6.3 Units/L and 8.4 Units/L. During that admission he was initially treated for acute coronary syndrome with heparin and due to continued negative troponin levels ACS was ruled out. An echocardiogram at that time demonstrated severe aortic stenosis. His chest pain was attributed to severe aortic stenosis and he underwent cardiac catheterization prior to surgical valve replacement. Coronary angiogram revealed mild non obstructive coronary artery disease. He is currently on multiple cardiovascular drugs and has a forty pack year history of smoking. His family history is significant for coronary artery disease. No history of muscular dystrophy in the family. Physical examination revealed no evidence of a primary muscle disorder or connective tissue disease. Further investigations including urinalysis, hematology screen, inflammatory markers, liver, renal and thyroid tests were all normal. The patient was monitored overnight with serial CK-MB levels and in the morning his chest pain had improved. In the view of his serial normal Troponin levels and electrocardiogram, myocardial infarction in this patient was ruled out and his elevated CK-MB was attributed to severe concentric hypertrophy of left ventricle.

Discussion:

Creatine kinase (CK) is a muscle enzyme which exists in three recognized isoenzymes: CK-MM (skeletal muscle); CK-MB (myocardium); and CK-BB(Brain) [1]. Around 90% of CK-MB is found in the myocardium but trace amounts are found in small intestine, tongue, diaphragm, and uterus. These isoenzymes are present in the cytosol and aid in the transfer of high energy phosphates into and out of mitochondria, thus helping in regeneration of ATP in

the cells. The normal blood levels of CK in males are 38 - 174 units/L and in females are 96 - 140 units/L. Normal level of CK-MB is less than 5 % of total CK. Elevation of CK can be associated with many conditions but primarily cardiac and muscle diseases. Myocardial injury usually results in CK-MB levels higher than 5% of total CK in the blood whereas skeletal muscle injury results in CK-MB levels lower than 5% of total CK. As a result, percentage criteria (2.5- 5%) have been proposed to distinguish skeletal muscle damage from cardiac damage. Occasionally, there are conditions where isolated CK-MB elevation or false elevation may be seen and diagnosed as an acute coronary syndrome.

There are several causes of isolated elevation of CK-MB, which an astute physician should be aware of. Hypertrophied myocardium is sometimes noted to have normal total CK but abnormally high CK-MB levels. These patients have decreased CK-MM activity and abnormally high CK-MB activity and thus present as elevated CK-MB and normal total CK [2]. In human myocardial biopsy material, concentrations of CK-MB have been reported to be 100-fold greater in patients with aortic stenosis, coronary artery disease, and coronary artery disease with left ventricular hypertrophy compared to patients without such findings. The pathophysiological basis for the above causes is by creating a state of myocardial hypoxia which causes heart to respond to augmented workload by increasing its mass and thus leading to elevated CK-MB concentration.

Another reason for elevated CK-MB levels is extreme physical activity, leading to aggressive muscle regeneration [3]. This leads to an increase in the proportion of the CK-MB in skeletal muscle, induced by endurance training. Elevated CK-MB may also be seen due to left ventricular hypertrophy secondary to aggressive physical training. Increased volume and pressure loads during intensive training can result in varying degrees of cardiac chamber enlargement, increased ventricular wall thickness, and reduced heart rate, constituting Athlete's Heart Syndrome (AHS). AHS is a benign syndrome and it has been demonstrated that the cardiac changes reverse within a few months of ceasing athletic training. The main clinical significance of AHS is that it can mimic significant cardiovascular disease, thus this needs to be kept in mind while suspecting cardiac disease in athletes.

Falsely elevated CK-MB has also been noted in certain malignancies, where the solid tumor is the source of the circulating CK-MB [4-6]. Markedly elevated circulating levels of CK-MB or increased levels of CK-MB in combination with CK-BB may point away from a myocardial source, and toward the existence of a malignancy. Thus it is necessary to do non-invasive screening tests to exclude a malignancy in patients with elevated CK-MB fractions without evidence of cardiac or muscle disease. These could include urinalysis, faecal occult blood, colonoscopy, prostate specific antigen, CA-125, CEA, chest x-ray, mammogram, and pelvic ultrasound.

Moderate to marked CK-MB elevations are noted in inflammatory myopathies (eg, polymyositis, dermatomyositis), muscular dystrophies (type 1), collagen vascular diseases (SLE) and scleroderma [7]. In these disease processes, in response to muscle fiber damage, muscle regeneration occurs, mainly during this regenerative process. Skeletal muscle fibers revert to an embryonic isoenzyme pattern and CK-MB is produced leading to increased levels (10 to 50% of total CK) [8]

Hypothyroidism is also known to increase CK-MB fraction, especially if associated with renal failure. It is well documented that hypothyroidism can cause persistent elevation of cardiac enzymes , the cause of which may be the leakage of the enzymes from the myocardial cells secondary to increased cell permeability . These Elevated cardiac enzymes (CK & CK-MB) in patients with hypothyroidism resolve with thyroid hormone replacement.[9]

False elevations of CK-MB may also be seen in chronic dialysis patients without acute ischemic heart disease. Chronic dialysis is associated with abnormal protein metabolism; muscle wasting; and decreased renal clearance. All of the above process may play a role in elevated CK-MB levels in these patients. [9-11]

Pulmonary Embolism may result in a dilated overloaded right ventricle, due to which there is increase in right ventricular oxygen demand and diminished perfusion of right coronary artery, thus leading to hypoxia and elevation of cardiac enzymes including troponins. [12]

High dose albuterol use in the treatment of asthma has shown transient elevation of CK-MB levels. Repeated nebulization events can exert an influence on cardiac muscle and this effect is probably connected with adrenergic stimulation [13].

One to two percent of the normal healthy population and people with ulcerative colitis, Bladder cancer or Prostrate cancer may have Macro-CK type 1, which has electrophoretic properties similar to CK-MB, presenting as false elevation of CK-MB [14]. Most assays measure CK-MB mass which avoids, for the most part, detection of macrokinases that can confound diagnosis with activity assays. Thus the presence of macrokinases should be considered, as one possibility, when CK-MB is a very high percentage (>20 percent) of total CK[15-17]. Dual-site murine antibody-based immunoassays are commonly used in clinical laboratories to quantitate the MB isoenzyme of creatine kinase (CK-MB). Heterophile antibodies (e.g., human anti-murine antibodies) can interfere with these assays and produce erroneous results. Adding heterophile blocking reagent in the serum can eliminate these false positive CK-MB [18] . New generation radio-immunoassays for CK-MB directly measure the isoenzyme level with antibodies that cross-react with MB or with auto antibodies to CK-MB itself. These are extremely sensitive and are sometimes able to detect small amounts of B-chain of CK protein along with CK-MB isoenzyme that is

present in skeletal muscle and can be reflected as elevated CK-MB[4] .

Conclusion

Total CK and CK-MB typically begin to rise 4-6h after the onset of infarction but is not elevated in all patients until about 12 hours. If initial measurement of CK and CK-MB are indeterminate, and the ECG is not diagnostic, clinicians should evaluate a series of measurements obtained over the first 24 hrs. Skeletal muscle release of CK-MB typically produces a "plateau" pattern, whereas acute MI produces a CK-MB elevation that peaks approximately 20 hours after the onset of coronary occlusion. An elevated serum CK-MB is relatively specific for myocardial injury, particularly in patients with ischemic symptoms when skeletal muscle damage is not present. These elevations return to baseline within 36-48h compared to durations as long as 10 days seen with troponin. Thus CK-MB, unlike troponin, cannot be used for the late diagnosis of an acute MI but can be used to suggest infarct extension if levels rise again after declining. Isolated elevation of CK-MB is a common occurrence in clinical practice and above mentioned factors should be kept in mind before labeling a diagnosis of acute coronary syndrome and exposing the patient to the risks of treatment with anticoagulation and invasive procedures. Careful consideration of the clinical presentation, ECG findings, other markers such as Troponin and the typical rise and fall of cardiac enzymes associated with myocardial infarction should help reduce such errors.

References

1. Bessman SP, Carpenter CL. The creatine-creatine phosphate energy shuttle. *Annu Rev Biochem* 1985;54:831-62.
2. Ingwall JS, Kramer MF, Fifer MA et al. The creatine kinase system in normal and diseased human myocardium. *N Engl J Med* 1985 October 24;313(17):1050-4.
3. Siegel AJ, Silverman LM, Evans WJ. Elevated skeletal muscle creatine kinase MB isoenzyme levels in marathon runners. *JAMA* 1983 November 25;250(20):2835-7.
4. Dickey W, Carson CA, Andrews WJ, Crowe PF. Apparent elevation of serum CK-MB not due to acute myocardial infarction. *Br J Clin Pract* 1992;46(2):149-50.
5. Wang HC, Lu JY, Ting YM. Elevated serum CK-MB and CK-BB isoenzymes in a patient with small cell lung cancer: a case report. *Zhonghua Yi Xue Za Zhi (Taipei)* 1995 March;55(3):270-3.
6. Wright SA, Liggett NW. Elevation of creatine kinase as a marker of malignancy. *Ir Med J* 2003 July;96(7):217.
7. Larca LJ, Coppola JT, Honig S. Creatine kinase MB isoenzyme in dermatomyositis: a noncardiac source. *Ann Intern Med* 1981 March;94(3):341-3.
8. Adornato BT, Engel WK. MB-creatine phosphokinase isoenzyme elevation not diagnostic of myocardial infarction. *Arch Intern Med* 1977 August;137(8):1089-90.
9. Strachan SR, Afolabi O, Brown N, Gray D. Chest pain, enzymes and hypothyroidism. *Postgrad Med J* 2000 March;76(893):168-9.
10. Jaffe AS, Ritter C, Meltzer V, Harter H, Roberts R. Unmasking artifactual increases in creatine kinase isoenzymes in patients with renal failure. *J Lab Clin Med* 1984 August;104(2):193-202.
11. Martinez-Vea A, Montoliu J, Company X, Vives A, Lopez-Pedret J, Revert L. Elevated CK-MB with normal total creatine kinase levels in patients undergoing maintenance hemodialysis. *Arch Intern Med* 1982 December;142(13):2346.
12. Smith SC, Ladenson JH, Mason JW, Jaffe AS. Elevations of cardiac troponin I associated with myocarditis. Experimental and clinical correlates. *Circulation* 1997 January 7;95(1):163-8.
13. Katz RW, Kelly HW, Crowley MR, Grad R, McWilliams BC, Murphy SJ. Safety of continuous nebulized albuterol for bronchospasm in infants and children. *Pediatrics* 1993 November;92(5):666-9.
14. Z'Graggen WJ, Wehrli C, Gautschi K, Alex V, Conen D. [Differential diagnostic considerations in CK-MB level increase]. *Praxis (Bern 1994)* 2000 November 9;89(45):1864-7.
15. Adams JE, III, Abendschein DR, Jaffe AS. Biochemical markers of myocardial injury. Is MB creatine kinase the choice for the 1990s? *Circulation* 1993 August;88(2):750-63.
16. Jay DW. Macro-creatine kinase co-migrating with CK-MB on electrophoresis. *Clin Chem* 1988 September;34(9):1920.
17. Sturk A, Sanders GT. Macro enzymes: prevalence, composition, detection and clinical relevance. *J Clin Chem Clin Biochem* 1990 February;28(2):65-81.
18. Sosolik RC, Hitchcock CL, Becker WJ. Heterophilic antibodies produce spuriously elevated concentrations of the MB isoenzyme of creatine kinase in a selected patient population. *Am J Clin Pathol* 1997 May;107(5):506-10.