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A Review Article in:

Assessment of the level of creatine phosphokinase in myocardial infarction

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Abstract

Cardiovascular diseases is a global and ancient health issue. Ischemic heart diseases are group of diseases including myocardial infarction and stable and unstable angina. The myocardial necrosis is accompanied by release of many chemicals that can serve as biomarkers. Creatine phosphokinase is the oldest cardiac enzyme discovered and was used a lot in the past as reliable diagnostic tool but now it use declined drastically due to the discovery of more specific and reliable tools like cardiac troponins. In this short review we will demonstrate the biochemistry , clinical significance and the efficacy in comparison to other cardiac biomarkers.

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1. Introduction

Dawn of the 21st century has witnessed the emergence of cardiovascular disorders as the leading cause of death globally, which entails a spectrum of disorders such as coronary or ischemic heart diseases, strokes, hypertensive heart diseases, inflammatory heart diseases, and rheumatic heart diseases [(1)]. Ischemic heart diseases are a group of diseases including myocardial infarction (MI) and stable and unstable angina. Over the past few decades, drastic changes in lifestyle such as lack of physical activity, stress, and obesity have led to life threatening conditions such as acute myocardial infarction (AMI) as a major cause of death in industrialized nations as well as in the developing world. Myocardial necrosis is accompanied by the release of structural protein and other intracellular macromolecules when the integrity of the cellular membranes is compromised, and then these biomarkers such as creatine phosphokinase (CPK), Creatine Kinase (CK)-MB, Cardiac-specific troponin T (cTnT), and cardiac-specific troponin I (cTnI) enter the blood stream and are measured in serum aiding in the detection of MI [(2)].

Creatine phosphokinase (CPK), also known by the name creatine kinase (CK) is the enzyme that catalyzes the reaction of creatine and adenosine triphosphate (ATP) to phosphocreatine and adenosine diphosphate (ADP). The phosphocreatine created from this reaction is used to supply tissues and cells that require substantial amounts of ATP like the brain, skeletal muscles, and the heart with their required ATP. The normal CPK level is considered to be 20 to 200 IU/L. Many conditions can cause derangement in CPK levels, including rhabdomyolysis, heart disease, kidney disease, or even certain medications [(3)].

The creatine kinase reaction was first identified in 1934 by K Lohman in the muscle tissue and it has undergone intensive investigation for over 80

years. The enzyme is of clinical importance and its levels are routinely used as an indicator of acute myocardial infarction [4].

It is the most widely used screening enzyme test for children presenting with muscular weakness, myalgia or developmental delay. CK, though more sensitive and specific than other muscle enzymes (lactate dehydrogenase, aldolase, transaminases (aspartate transaminase, alanine transaminase) can create diagnostic uncertainties when raised in certain neuronal diseases and may be normal in some muscular conditions. Interpretation of CK level should be guided by the clinical picture. In certain muscle conditions, it may also aid monitoring of disease progression and response to treatment [5].

In this short article, we will emphasize the role and assessment of creatine phosphokinase in management of myocardial infarction.

2. Literature review

Creatine kinase (also known as: Adenosine-5–triphosphate; creatine phospho transferase; creatine phosphokinase; phosphocreatine phosphokinase; creatine *N*-phosphotransferase; (EC 2.7.3.2)) catalyzes the reversible transfer of a phosphoryl group from MgATP to creatine (Cr), producing phosphocreatine (PCr) and MgADP. CK is a highly conserved enzyme of 40 kDa, with its sequence being ~60% identical across all species and isoforms. It is a member of the phospahgen kinase family of guanidino kinases (ATP-guanidino-phosphotransferases) [6]. Creatine kinase (CK) is an enzyme expressed in high amounts in muscle tissues, with three isoenzymes: CK-MM (creatine phosphokinase skeletal muscle), CK-BB (creatine phosphokinase brain band), CK-MB (creatine phosphokinase myocardial band). CK-BB is found in brain tissue, CK-MM

in skeletal tissue, while CK-MB is specific to myocardial cells although it is also found in skeletal muscle. Elevated CK-MB levels have high specificity for myocardial infarction, early clearance helping in the detection of re-infarction [7].

Elevated levels of CK-MB have been associated with higher mortality rates in AMI patients. Furthermore, in patients undergoing percutaneous coronary interventions (PCI), elevated CKMB levels continue to be associated with increased mortality at the three-month, six-month and one-year follow-up [8].

After passing into the blood, CK-MB is divided into two groups as MB1 and MB2. In the plasma, the CK subtypes are normally in equilibrium. When AMI occurs, MB2 passes into blood with a low ratio and a significant change in the MB2:MB1 ratio occurs, whereas CK and CK-MB levels remain normal. An MB2:MB1 ratio ≥1.5 is interpreted in favor of AMI [9].

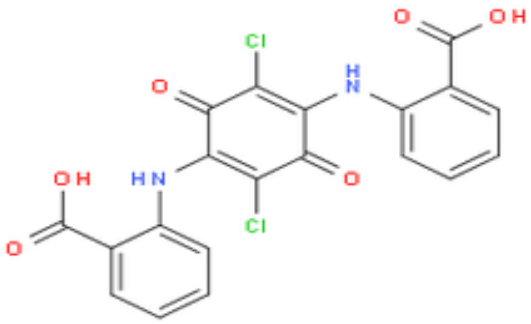

Figure 1. Creatine kinase structure

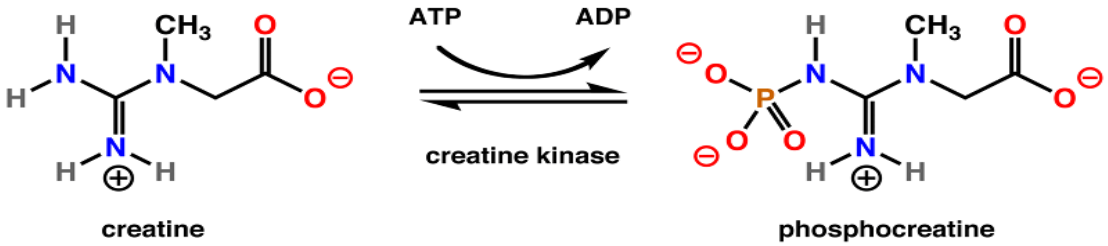

Figure 2. Function of creatine kinase

For many years the main physiological role ascribed to CK was the maintenance of energy homeostasis at sites of high energy turnover such as rapidly contracting skeletal muscle cells. The discovery of the existence of creatine kinase isoenzymes in different cellular locations led to the hypothesis that fosfocreatine had several functions in skeletal muscle. One of these functions was to mantain constant levels of ATP and ADP, buffering the cell against rapid depletion of ATP. The discovery of the mitochondrial isozymes demonstrated that CK was located in different compartments and the concept of a phosphocreatine shuttle was developed: a system power transmission between the local production of ATP (mitochondria) and the place of use (in generally, the myofibrils), where distinct isoenzymes are associated with sites of ATP production and consumption, acting as a transport mechanism for high energy phosphates [(10)].

3. Clinical importance of CPK enzyme

Creatine kinase activity is one of the oldest markers of acute myocardial infarction (AMI). Creatine kinase activity begins to rise within 12 hours of AMI symptoms, peaks at 24 to 36 hours and normalizes after 48 to 72 hours. The issue with measuring creatine kinase activity for AMI is that it is not specific to the heart. CK activity can increase in several conditions such as rhabdomyolysis, chronic muscle diseases, burns, and even after

strenuous exercise. Thus, the CK-MB isoenzyme started being used to aid in the diagnosis of AMI. Although the CK-MB measurement is an improvement over just CK, it can still become increased in other conditions such as acute muscle injury, congestive cardiac failure, and arrhythmias [11].

Patients with Alzheimer disease and Pick disease may have decreased CPK activity in the brain. The BB-CK activity is primarily decreased in these patients, resulting in an overall decrease in total CPK activity as well. CPK levels also elevate in patients with rhabdomyolysis. A CPK level which increases to more than 1000 IU/L is indicative of rhabdomyolysis; values over 5000 IU/L indicate severe rhabdomyolysis. Patients with sickle cell trait who suddenly start a new strenuous exercise program such as spin class are also at an increased risk of rhabdomyolysis, with reported levels of creatine kinase higher than 70000 IU/L in some cases. The most common complication resulting from rhabdomyolysis is acute kidney injury. Therefore, any patient that comes with suspected rhabdomyolysis should receive prompt treatment with intravenous fluids to preserve kidney function [12].

Patients on statins such as simvastatin may have an adverse effect of significantly elevated CPK levels which can also lead to rhabdomyolysis. This adverse effect becomes amplified if the patient also receives a concurrent drug that inhibits cytochrome P450-3A4 (CYP3A4). Some common medications to avoid in patients on statin therapy include clarithromycin, erythromycin, verapamil, tamoxifen, and many antifungal agents. Low levels of CPK can be present in patients with connective tissue diseases such as rheumatoid arthritis or systemic lupus erythematosus. There may also be low levels in patients that have reduced physical activity such as elderly bedridden patients [13].

4. Normal values

Total creatine phosophokinase (CPK) (14)

Adult/elderly:

- Male: 55-170 units/L or 55-170 units/L (SI units)
- Female: 30-135 units/L or 30-135 units/L (SI units)

(Values are higher following exercise.)

Newborn: 68-580 units/L (SI units)

Isoenzymes:

- Creatine kinase-MM (CK-MM): 100%
- CK-MB: 0%
- CK-BB: 0%

However, serum CK levels can vary among healthy subjects, even when correcting for muscle mass. Age, gender, race, and, as stated, physical activity can affect CK. CK is higher among black males, as well as newborns. Moreover, CK reference ranges are varied with different assays and reference [14].

5. Diagnosis of acute myocardial infarction in patients

The diagnosis of AMI, as formally established by the world health organization, requires at least two of the following criteria: a history of chest pain, evolutionary changes on the ECG, and elevation of serial cardiac enzymes. Often, the examining physician is fairly certain after obtaining a patients history and completing a physical examination and performing ECG that an MI has occurred. When the ECG fails to demonstrate an AMI, the cardiac markers must be used [15]. Various cardiac markers have been proposed to date some of them are Creatine Kinase (CK); Lactate dehydrogenase (LD); Cardiac Troponin-I and Troponin-T; Myoglobin; Cholesterol; Triglycerides; Low density lipoprotein (LDL); High-density lipoprotein HDL. An initial creatine

kinase isoenzyme-2 (CK-2) rise takes 4 to 6 h to increase above the upper reference limit. Peak levels occur at approximately 24h. Return to normal takes 48 to 72h. Factors that might affect the classic pattern include size of infarction, CK-2 composition in the myocardium, concomitant skeletal muscle injury, and reperfusion (spontaneous; following thrombolytics, or following angioplasty) [16].

CK-MB measurement began to gain attention as a biomarker for myocardial damage in 1970s. However, with the availability of troponin assays in 2000s, troponin has become the biomarker of choice. In 2014, joint guidelines from American Heart Association (AHA) and American College of Cardiologists (ACC) considered the value of CK-MB not to be high enough to warrant testing if contemporary troponin assay is available. However, the use of CK-MB testing is still widespread in suspected ACS cases despite the current guidelines [17-18].

(CK-MB) or troponin measurements are often performed in clinical practice, and the peak values have been shown to reflect infarct size and clinical outcome. Although some studies have reported the relation between cardiac biomarkers, such as CK-MB and troponins, and infarct size by cMRI, there is little evidence about patients with first anterior STEMI and large territories at risk but who underwent reperfusion [19].

6. The role of CK in determining the infarct size

Infarct size is one of the most important prognostic markers after acute myocardial infarction (AMI). Possibilities to assess infarct size non-invasively include imaging methods, electrocardiographic analysis and cardiac biomarkers. Although CE-CMR is highly reliable in detecting infarct size and quantifying LV function, it is an expensive procedure that is time consuming and mostly available only in dedicated centers. By contrast, simple biochemical markers, such as cardiac troponins (cTnT and

cTnI) and creatine kinase (CK), are cost-effective tools in clinical routine to assess myocardial damage. Moreover, large trials have shown the predictive value of elevated cTnT/cTnI and CK(-MB) [20].

In a randomized clinical trial, it was demonstrated that peak CK-MB values were significantly and positively correlated with infarct size and inversely related to LVEF in patients who underwent primary PCI for the first anterior STEMI. Furthermore, peak CK-MB was a powerful independent predictor of not only LV dysfunction but also of 1-year clinical outcomes. The current results provide substantial support for using peak CK-MB as a simple and reasonably accurate surrogate for infarct size and LV dysfunction in large anterior STEMI [21].

7. Creatine phosphokinase vs Troponins

CK-MB still holds some diagnostic value in cardiac and non-cardiac conditions. CK-MB is detected in the serum 4 hours after myocardial injury, peaks by 24 hours, and normalizes within 48 to 72 hours. CK-MB is a useful biomarker for detecting acute MI as it has a relative specificity for cardiac tissue but can still become elevated in non-cardiac conditions such as skeletal muscle injury, hypothyroidism, chronic renal failure, and severe exercise. The ratio of CK-MB2 to CK-MB1 greater than or equal to 1.5 and a CK-MB relative index (CK-MB/total CK x 100) greater than or equal to 2.5 improve specificity for cardiac tissue and are indicative of acute MI [22].

Since CK-MB normalizes 48 to 72 hours after myocardial ischemia (vs. troponins, which can persist for days), it can be useful in detecting re-infarction if levels rise again after declining [22]. Troponin T and troponin I levels in the blood rise as early as 4 hours from the onset of acute MI symptoms, peaks in 24 to 48 hours, and remain elevated for multiple

days thereby making them useful for detecting initial ischemic events but not reliable to detect re-infarction. High-sensitivity troponin assay (hs-TnT), a test developed to detect troponin at much lower concentrations than what the conventional troponin tests can detect, allows for more rapid diagnosis in patients admitted to the hospital suspected to have acute MI [23].

8. Non-acute MI Causes of CK-MB Elevation

The skeletal muscle and myocardial cell death of any etiology will cause an elevation of CK-MB. Listed below are multiple other causes of CK-MB elevation in plasma. False elevations in CK-MB occur in the presence of atypical CK isoforms, macrokinases, and adenylate kinase; however, these false elevations can be eliminated by adding reagents to testing kits.

Cardiac etiology - myocarditis, cardiac surgery can damage heart muscle resulting in elevation of CK-MB.

Peripheral sources - rhabdomyolysis, myositis, inflammatory myopathies, trauma, medications (daptomycin, statins, antiretrovirals)

To differentiate the elevation of CK-MB for cardiac etiology versus skeletal muscle source, we can calculate the CK-MB relative index (CK-MB RI) by using the below formula.

- **CK-MB RI = CK-MB (ng/mL) /CK (ng/mL) X 100**

A CK-MB relative index < 3% is consistent with the skeletal muscle source, whereas a relative index > 5% is consistent with the cardiac source of CK-MB. However, prior studies in patients with trauma and patients with chronic skeletal muscle abnormalities have demonstrated the failure of CK-MB Relative index in differentiating skeletal muscle sources of CK-MB from myocardial cell death.

Hence in patients with clear evidence of lack of trauma, chronic skeletal muscle abnormalities, and a high index of suspicion for AMI, the use of CK-MB RI can increase the specificity of CK-MB testing. Miscellaneous causes include hypothyroidism, renal failure, alcohol intoxication, pregnancy, and certain types of malignancies [24].

9. Conclusion

Creatine phosphokinase was the first reliable tool for assessment of the cardiac events but now it use decreases significantly after the discovery and use of cardiac troponins and other biomarkers.

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