



CREATINE KINASE MB/ (CK-MB)

Intended Use

The i-STAT® CK-MB test is an *in vitro* diagnostic test for the quantitative measurement of creatine kinase MB mass in whole blood or plasma samples. CK-MB measurements can be used as an aid in the diagnosis and treatment of myocardial infarction (MI).

Method Explanation

The i-STAT CK-MB test cartridge uses a two-site enzyme-linked immunosorbant assay (ELISA) method. Antibodies specific for an epitope unique to the CK-MB subunit, that therefore do not bind CK-MM or CK-BB, are located on an electrochemical sensor fabricated on a silicon chip. Also deposited in another location on the sensor silicon chip is an antibody/alkaline phosphatase enzyme conjugate specific to an epitope on the B subunit of creatine kinase. The specificity of the conjugate antibody to the B subunit allows this conjugate to recognize CK-MB and CK-BB, but not CK-MM. The whole blood or plasma sample is brought into contact with the sensors allowing the enzyme conjugate to dissolve into the sample. The CK-MB within the sample becomes labeled with alkaline phosphatase and is captured onto the surface of the electrochemical sensor during an incubation period of approximately three minutes. The sample is washed off the sensors, as well as excess enzyme conjugate. Within the wash fluid is a substrate for the alkaline phosphatase enzyme. The enzyme bound to the antibody/antigen/antibody sandwich cleaves the substrate releasing an electrochemically detectable product. The electrochemical (amperometric) sensor measures this enzyme product which is proportional to the concentration of CK-MB within the sample.

Contents

Each i-STAT CK-MB cartridge provides a sample inlet, sensors to detect the CK-MB as described above, and all the necessary reagents needed to perform the test. The cartridge contains a buffer and preservatives. A list of reactive ingredients is indicated below:

Reactive Ingredient	Biological Source	Minimum Quantity
Antibody/Alkaline Phosphatase Conjugate	Murine IgG : Bovine Intestine	0.013 µg
IgG	Caprine IgG : Murine IgG	4 µg
Sodium Aminophenyl Phosphate	N/A	0.9 mg
Heparin	Porcine Intestine	0.45 IU

Metrological Traceability

The i-STAT System test for creatine kinase-MB (CK-MB) measures creatine kinase-MB amount-of-substance concentration mass in plasma or the plasma fraction of venous whole blood (dimension ng/mL) for *in vitro* diagnostic use. Creatine kinase-MB values assigned to i-STAT System controls are traceable to the American Association of Clinical Chemists (AACC recombinant human CK-MB from Seradyn Inc.) calibrator for the standardization of creatine kinase mass assays. i-STAT System controls and calibration verification materials are validated for use only with the i-STAT System and assigned values may not be commutable with other methods. Further information regarding metrological traceability is available from Abbott Point of Care Inc.

Reportable Range

The i-STAT CK-MB test will report 0.0 to 150.0 ng/mL ($\mu\text{g/L}$). Samples above the reportable range will yield ">150.0 ng/mL" on the analyzer display screen.

Reference Range

Whole blood and plasma samples from 161 apparently healthy donors were assayed in duplicate using three different lots of i-STAT CK-MB cartridges. The 0 to 95% range of results spanned 0.0 ng/mL ($\mu\text{g/L}$) to 3.5 ng/mL ($\mu\text{g/L}$).

Note: Each facility should establish its own reference range using the i-STAT CK-MB assay.

Clinical Significance

CK-MB mass has been reported to be useful for the diagnosis of myocardial infarction, re-infarction, and the sizing of infarction.

For optimal diagnostic usefulness, a cardiac marker should be specific for cardiac tissue, should be rapidly released into the bloodstream with a direct proportional relationship between the extent of myocardial injury and the measured level of the marker, and should persist in blood for a sufficient length of time to provide a convenient diagnostic time window.¹

Creatine kinase (CK) is a dimeric enzyme found primarily in brain and muscle tissue. There are three isoforms of creatine kinase: BB, MM, and MB. BB is found primarily in the brain. Skeletal muscles primarily contain the MM isoform, with traces of MB (estimates of 1-4% of CK activity). Cardiac muscles also contain primarily the MM isoform, but higher amounts of MB, typically around 20% of CK activity.² Serum from healthy individuals typically contains the MM isoform and a small amount of the MB isoform. CK-MB can be released into the bloodstream by a number of actions, including skeletal muscle injury and myocardial damage.

The rise in CK-MB in the bloodstream occurs between 4-6 hours following a myocardial infarction (MI). The concentration peaks after approximately 24-hours and returns to baseline after 36-72 hours. As the level of CK-MB is not cardiac specific, the results of a single test are not indicative of a myocardial infarction (MI). Typically an MI is diagnosed based on the pattern of CK-MB analyses taken at 3-hour intervals for a 6- to-9 hour period or at 6- to-8 hour intervals for a 24-hour period.

Although the cardiac-specific troponins, troponin I (cTnI) and troponin T (cTnT) are now considered the biochemical markers of choice in the evaluation of acute coronary syndromes (ACS) including ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, and unstable angina, CK-MB can also be used as a secondary marker to aid in the diagnosis of myocardial infarction and measuring the degree of myocardial necrosis. Since low levels of CK-MB can be detected in the blood of healthy persons, any CK-MB value above the 95th percentile may be indicative of some degree of myocardial necrosis.¹ Each institution should establish its own reference range for its patient population, and this range should be used to determine an appropriate limit indicative of acute myocardial infarction (AMI).

The European Society of Cardiology / American College of Cardiology consensus document notes that in the clinical setting of a reinfarction, CK-MB may be more useful for monitoring for MI than cardiac troponin I (cTnI) or cardiac troponin T (cTnT) because CK-MB remains increased for only 2-4 days following an MI,

in contrast to up to 5 days for cTnl or 10 days for cTnT.^{3,4,5,6,7} Clinical studies have also demonstrated a close relationship between the extent of injury to the myocardium (infarct size) following MI and increased serum CK-MB mass concentrations.⁸ Similarly, significant correlations have been observed between CK-MB estimated infarct sizing and left ventricular echocardiography.⁸

Other conditions involving skeletal muscle damage like accidents, blunt trauma, severe burns, and extreme exercise or myopathic disorders such as myocarditis that are not secondary to ischemic coronary artery disease can also lead to skeletal muscle or myocardial injury and have the potential to cause elevations in the blood concentrations of CK-MB. These conditions should be considered when interpreting results, and the CK-MB level should be used in conjunction with clinical symptoms, signs, patient history, and ECG changes.^{1,9}

Performance Characteristics

Precision data were collected in multiple sites as follows: Duplicates of each control were tested daily for a period of 20 days for each of three lots of cartridges, resulting in a total of 120 replicates. The average statistics are presented below.

Method comparison data were collected using CLSI guideline EP9-A2.¹⁰ Venous blood samples were collected in heparinized evacuated tubes and analyzed in duplicate on the i-STAT System. A portion of the specimen was centrifuged and the separated plasma was analyzed in duplicate on the i-STAT System and on the comparative method within 1 hour of collection.

Deming regression analysis¹¹ was performed on the first replicate of each sample. In the method comparison table, n is the number of specimens in the first data set, Sxx and Syy refer to estimates of imprecision based on the duplicates of the comparative and the i-STAT methods, respectively. Sy.x is the standard error of the estimate, and r is the correlation coefficient.*

Method comparisons may vary from site to site due to differences in sample handling, comparative method calibration and other site specific variables.

Interference studies were based on CLSI guideline EP7-A.¹²

*The usual warning relating to the use of regression analysis is summarized here as a reminder. For any analyte, "if the data is a narrow range, the estimate of the regression parameters are relatively imprecise and may be biased. Therefore, predictions made from estimates may be invalid",¹⁰ The correlation coefficient, r, can be used as a guide to assess the adequacy of the comparative method range in overcoming the problem. As a guide, the range of data can be considered adequate if $r > 0.975$.

Precision Data (ng/mL)

Plasma Control	Mean	SD	%CV
Level 1	5.9	0.7	11.9
Level 2	25.8	2.7	10.4
Level 3	90.1	9.0	10.0

Method Comparison (ng/mL)

Abbott AxSYM

n	263
Sxx	1.84
Syy	2.66
Slope	1.01
Int't	-0.19
Sy.x	3.98
Xmin	0.04
Xmax	224
r	0.994

Analytical Sensitivities

The sensitivity of the CK-MB method is 0.6 ng/mL, which is the lowest CK-MB level that can be distinguished from zero. The analytical sensitivity is defined as two standard deviations associated with a zero calibrator. The analytical sensitivity was estimated using a control material with <1 ng/mL CK-MB during a 20-day precision study in which three separate lots of CK-MB test cartridges were tested in duplicate using a pool of six i-STAT 1 analyzers for a total of 120 test results.

Analytical Specificity

The CK-MB method is specific for the creatine kinase MB isoenzyme. The following muscle proteins were tested and found to have an insignificant effect on the measured CK-MB.

Crossreactant	Concentration	Percent Crossreactivity
CK-MM (skeletal)	10000 ng/mL	Not Detectable
CK-BB (brain)	100 ng/mL	Not Detectable

Recovery

The dilution linearity of the i-STAT CK-MB test was investigated using heparinized whole blood and plasma samples derived from three separate donors. For each donor, the original CK-MB negative sample and a CK-MB spiked sample were prepared. This process yielded three CK-MB positive whole blood samples that were then assayed in duplicate for each of three separate i-STAT CK-MB cartridge lots. These whole blood samples were then diluted using an equal mass of the original unspiked whole blood and assayed in duplicate. From this whole blood data, the CK-MB recovery was calculated.

The plasma derived from these three donors was combined in equal masses and all pairwise combinations. These combinations were then assayed in duplicate for each of three separate i-STAT CK-MB cartridge lots. The CK-MB recovery for each pair was calculated using the average of the six results. The % recoveries are listed in the Tables below.

Whole Blood

Sample	Concentration (ng/mL)	Diluted Concentration (ng/mL)	% Recovery
A	73.24	40.73	108.7%
B	8.90	6.07	101.5%
C	47.74	26.91	109.3%

Plasma

Sample	Concentration (ng/mL)	Diluted Concentration (ng/mL)	% Recovery
A	73.24	—	—
B	8.90	—	—
C	47.74	—	—
A+B	—	42.17	102.7%
B+C	—	30.85	108.9%
A+C	—	63.95	105.7%

Test Limitations

The frequency of suppressed results is affected by atmospheric pressure. Suppressed result rates may increase with higher elevations (decreased barometric pressure) and may become persistent if testing is performed at more than 7500 feet above sea level. Where unavailability of results is unacceptable, i-STAT recommends having an alternate test method available.

Samples from patients who have been exposed to animals or who have received therapeutic or diagnostic procedures employing immunoglobulins or reagents derived from immunoglobulins may contain antibodies, e.g., HAMA or other heterophile antibodies, which may interfere with immunoassays and produce erroneous results.¹³⁻¹⁹ The generation of potentially interfering antibodies in response to bacterial infections has been reported.¹³ While this product contains reagents that minimize the effect of these interferents, and QC algorithms designed to detect their effects, the possibility of interference causing erroneous results should be evaluated carefully in cases where there are inconsistencies in the clinical information.

Partially clotted samples can result in elevated CK-MB readings above the reference range, as well as quality check code errors. To prevent this from occurring, upon drawing the whole blood sample into a heparinized collection tube, the sample should be inverted gently at least 10 times to ensure even dissolution of the heparin anticoagulant.

Grossly hemolyzed samples can cause a decreased alkaline phosphatase activity, resulting in decreased detection of CK-MB, increased assay backgrounds, and/or quality check codes.

Hematocrits in the range of 0-70% PCV have been demonstrated not to affect results. Samples with hematocrit levels above this range have demonstrated increases in the test imprecision and quality check codes.

The analyzer must remain on a flat surface with the display facing up during testing. Motion of the analyzer during testing can increase the frequency of suppressed results or quality check codes. A level surface includes running the handheld in the downloader/recharger.

Interference Testing

When added to a plasma pool containing approximately 20 ng/mL of creatine kinase MB isoenzyme, the following substances were found to have no significant effect (less than 10%) on the CK-MB method at the concentrations indicated.

Compound	Test Level ($\mu\text{mol/L}$ unless otherwise indicated)
Acetaminophen	1660
Allopurinol	294
Ampicillin	152
Ascorbic Acid	227
Acetyl Salicylic Acid	3330
Atenolol	37.6
Caffeine	308
Captopril	23
Chloramphenicol	155
Diclofenac	169
Digoxin	6.15
Dopamine	5.87
Enalaprilat	0.86
Erythromycin	81.6
Furosemide	181
Sodium Heparin	90 U/mL
Ibuprofen	2425
Isosorbide dinitrate	636
Methyldopa	71
Nicotine	6.2
Nifedipine	1156
Phenytoin	198
Propranolol	7.71
Salicylic Acid	4340
Theophylline	222
Verapamil	4.4
Warfarin	64.9

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