

Evaluation of albumin –cobalt binding as a specific test for assessment of myocardial infarction.

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Summary:

J Fac Med Baghdad
2007; Vol. 49, No.2
Received Jan. 2007
Accepted March 2007

Background : The new biological marker, ischemia modified albumin (IMA) measured by albumin cobalt binding (ACB) test was introduced for the detection of myocardial ischemia.

Objective The aim of the present study was to describe the performance characteristics of the ACB test in suspected acute coronary syndrome patients who presented to the emergency department early after the onset of ischemic events and to verify the specificity of the test for myocardial infarction .

Subjects and methods: Forty five patients presented to the emergency department (ED) with chest pain and 31 healthy controls were involved in the study. Serum albumin and ACB test were performed on all subjects, while serum CK-MB was done on patients with chest pain only.

The patients were diagnosed to have either myocardial infarction, MI (30) or unstable angina, UA (15). The sensitivity and specificity of the ACB test for the detection of ischemia were evaluated by ROC curve analysis.

Results and conclusion ACB test could be considered as an early test for myocardial ischemia and could detect ischemia much earlier than other cardiac markers. The significant negative predictive value of the test may play an important role in the rapid rule out of myocardial ischemia and will reduce the inappropriate admission of low risk patients. However it is a poor discriminator between patients with MI and those with UA.

Key words : Albumin Cobalt binding test , myocardial ischemia unstable angina.

Introduction :

Ischemia refers to lack of oxygen due to inadequate perfusion, which results from imbalance between oxygen supply and demand. The most common cause of myocardial infarction is atherosclerotic disease of epicardial coronary arteries. Acute myocardial infarction (AMI) generally occurs when coronary blood flow decreases abruptly after thrombotic occlusion of a coronary artery previously narrowed by atherosclerosis¹.

A steady decline in the rate of mortality from AMI has been observed across several population groups since 1960 caused by a fall in the incidence of AMI replaced in part by an increase in the rate of unstable angina^{2,3}. The coronary care unit phase began in the mid-1960s and was notable for detailed analysis and vigorous management of the cardiac arrhythmias⁴.

The diagnosis of AMI has traditionally relied upon the combination of chest pain and electrocardiographic (ECG) manifestations and elevations in serum markers of cardiac injury. The availability of new serum cardiac markers with markedly enhanced sensitivity for myocardial damage enables clinician to diagnose AMI in about

an additional one third of patients who would have fulfilled criteria for AMI in the past⁵.

As myocytes become necrotic the integrity of the sarcolemmal membrane is compromised and intracellular macromolecules (serum cardiac markers) begin to diffuse into the cardiac interstitium and ultimately into the micro-vascular and lymphatics in the region of the infarct⁶. Time of appearance of serum markers for acute MI varies from 1 -12 hours after the onset of chest pain.

Recently a new biological marker, Ischemia Modified Albumin (IMA) was introduced for detection of myocardial ischemia. It is measured by the albumin Cobalt binding (ACB) test. It is a very early indicator of myocardial ischemia which can occur within minutes of an ischemia event and could be detectable after 6 -12 hours^{7,8}.

The aim of the present study was to describe the performance characteristics of the ACB test in suspected acute coronary syndrome patients who were presented to the emergency department early after the onset of ischemic events and to verify whether the specificity of the test is confined to the MI (myocytes necrosis) or extended to involve whole myocardial ischemia (with or without myocytes necrosis) as in unstable angina.

Subjects and specimens :

The study involved 45 patients with chest pain or atypical symptoms suggestive of ischemic heart disease IHD presented to the emergency

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They were diagnosed later as 30 with myocardial infarction (MI) and 15 with unstable angina (UA).

Another 31 apparently healthy subjects with no history of cardiac problems were involved as a control group.

Ten milliliters of venous blood were drawn from each subject. For patients the blood was drawn at the time of admission to the casualty department. The samples were left to clot and centrifuged to obtain serum which was separated and used for measurement of ACB and CK-MB activity.

Methods :

The ACB test was done according to the method of Bar-Or et. al 2000, which is based on the premise that myocardial ischemia causes changes in human serum albumin that are demonstrated by reduced exogenous Co(II) bindings.⁹

Serum CK-MB was measured photometrically by using specific antibodies against CK-M which inhibit all CK-MM and CK-M of the CK-MB fraction and according to the DGKC (German Society of Clinical Chemistry) & IFC (International Federation of Clinical Chemistry).The test was performed on patients presented to the emergency department with chest pain and repeated for 15 MI patients 24 hours after admission.

Biostatistics methods :

- 1-Receiver operating characteristics (ROC) curves were used to compare the performance of two competing diagnostic tests and to obtain the appropriate cutoff value of those tests.
- 2- Student t-test for degree of significance.
- 3- ANOVA test for multi-comparison.
- 4- Correlation analysis.

Results :

Serum albumin was lower , but not significantly , in the 30 MI group of patients (4.2 ± 0.44 g / dL) and 15 unstable angina patients (4.4 ± 0.43 g /dL) as compared to the 31 normal control subjects (4.9 ± 0.6 g / dL).

Serum CK-MB was significantly higher in the MI group(32.4 ± 22.9 U/L) at the time of admission and 24 hours after(109.5 ± 69.4 U/ L) than the recommended normal value of less 24 U/L, with no change in the group of UA (8.8 ± 5.8 U/L). The mean absorbance units (ABSU) \pm SD of ACB test was 0.46 ± 0.09 for the controls , 0.6 ± 0.04 for the UA group & 0.59 ± 0.1 for the MI group. Performance of the ROC curve between all myocardial ischemia patients (MI & UA) and the

controls revealed that at a cutoff point of 0.51 ABSU the specificity and sensitivity of the ACB test were 74 % and 84 % respectively with an area under the curve of 0.87, (fig.1).

Relatively similar results were obtained after construction of the curve to each MI and UA groups separately with the control group. However ROC curve analysis revealed an area of 0.44 for MI against UA , (figs 2 & 3).

A significant negative correlation was seen between the ACB test and serum albumin concentration in the ischemic groups, MI & UA, (fig.4 & 5).

Discussion :

The ROC curve analysis performed between the ischemic group (combined MI & UA) and the non ischemic control group (fig.1) revealed a positive predictive value of 83 % and a negative predictive value of 77 % .These results confirm previous reports^{7, 9,10} .This implies that the ACB test can distinguish between myocardial ischemic patients and the non ischemic patients. This is very important ideally as it is essential to identify myocardial ischemia before the onset of irreparable myocardial cell damage¹⁰. In addition none of the traditional variables, 12-lead ECG, biochemical markers of necrosis and imaging techniques could be considered a true "gold standard" for the diagnosis of myocardial ischemia^{11,12}.

ROC curve analysis between MI and non ischemic controls(fig.2) showed that at the cutoff value of 0.51 the specificity and sensitivity were 74 % & 80 % respectively , the positive predictive value was 75 % while the negative predictive value was 80 % .The sensitivity of the ACB test for MI is considered reliable and important because detectable changes in ACB have been documented to occur minutes after transient occlusion and reperfusion of coronary artery during angioplasty¹³, while troponines and CK-MB exhibit a time course for release and detection in peripheral circulation. Therefore this biochemical marker (ACB) could serve as a good predictor of more specific and sensitive cardiac marker. Moreover Christenson et al (2001) demonstrated that ACB test might be an early predictor of cTnI positive or negative results 6 -24 hours later in acute coronary syndrome patients⁷, so the ACB test could bring a new dimension to the care of acute coronary syndrome patients and would add substantially to troponin measurements which have low diagnostic sensitivity (30 -50 %) in the first hours after presentation^{14,15} .

The specificity and positive predictive value of ACB test in the MI group were considered acceptable but were not ideal since this may lead to an overlap between high risk (disease) and normal control reference (non-disease) population but , however , this was also seen with numerous useful

diagnostic laboratory tests including total cholesterol, high-sensitivity C-reactive protein and total CK. Another study showed that the ischemia modified albumin has a high sensitivity for prediction of a discharge diagnosis of acute coronary syndrome, but comparatively low specificity, in contrast to the presentation of troponin which has high specificity but very low sensitivity; one of the reasons suggested for that is that the ischemia modified albumin can detect ischemia that is subclinical and beyond the ability of other conventional diagnostic methods to identify¹⁶.

The negative predictive value of ACB test in the MI group was reliable and significant in ruling out patients who do not have acute coronary syndrome, as there is about more than 50% of patients presenting to emergency department with chest pain are admitted to a hospital to rule out ischemic heart disease¹⁷.

A more or less similar ROC curve was obtained between UA and non ischemic patients (fig 3). This indicates that the ACB test is a poor discriminator between the MI & UA patients which confirms previous results¹⁰. However another study showed that ischemia modified albumin was higher in UA than MI without myocardial necrosis as compared with those with acute myocardial ischemia¹⁶.

The presence of a significant negative correlation between ACB and serum albumin in the ischemic patients (Figs 4 & 5) is considered logical as the basic principle of the test involves the N-terminal region of human serum albumin and its inherent affinity for the metal ion Co(II)¹⁰.

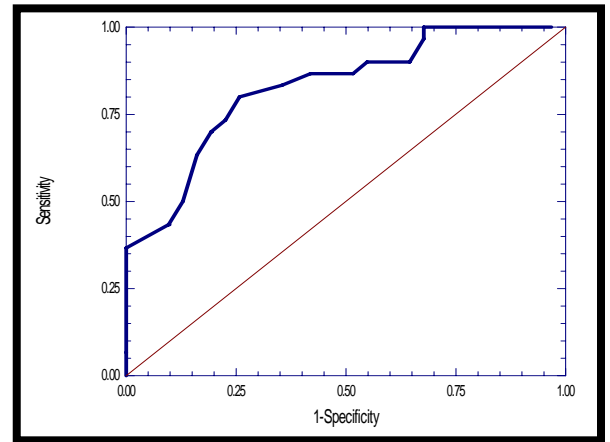


Figure (2): ROC curves derived for MI vs Control groups

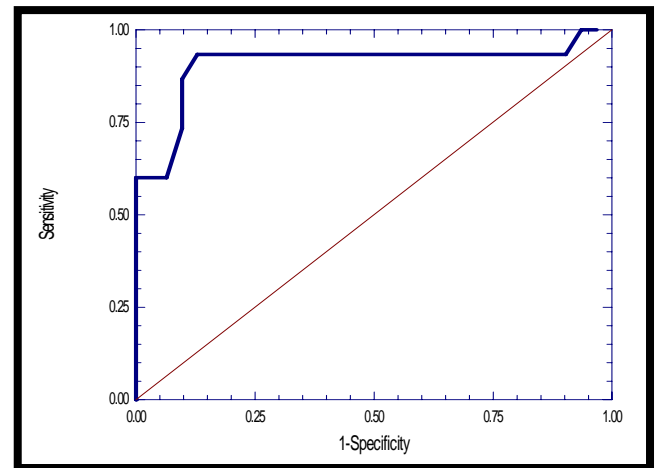


Figure (3): ROC curves derived for UA vs Control groups.

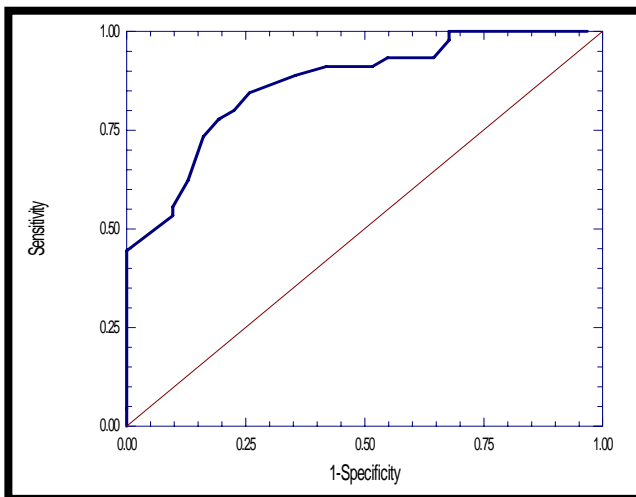


Figure (1): ROC curves derived for all ischemic vs control groups.

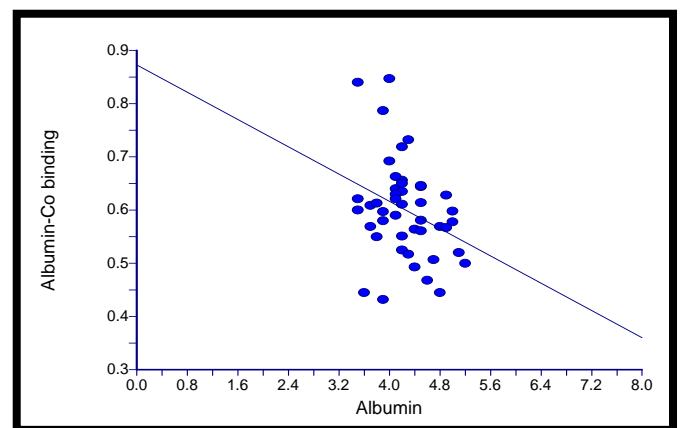


Figure (4): The Relationship between ACB assay and serum albumin in patients with ischemia ($r=-0.31$, $p=0.04$).

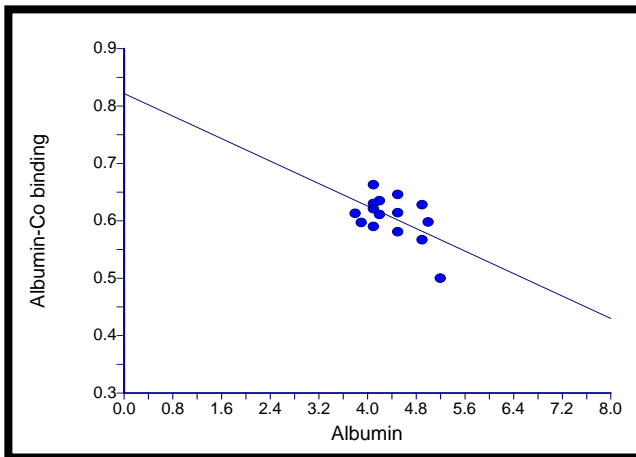


Figure (5): The Relationship between ACB assay and serum albumin in patients with unstable angina($r=-0.54$, $p=0.04$).

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