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ROLE OF ISCHEMIA MODIFIED ALBUMIN IN THE DIAGNOSIS OF ACUTE CORONARY SYNDROME

SHILPASREE AS¹, KIRAN KUMAR²

1. Assistant professor department of Biochemistry Subbaiah institute of medical sciences Shimoga India.
2. Professor department of Oral pathology Subbaiah institute of dental sciences Shimoga India.

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Abstract: Ischemia modified albumin (IMA) is generated as a result of myocardial ischemia due to the alteration in N terminal end of human serum albumin. IMA can be used in the diagnosis of acute coronary syndrome. Although the markers like cardiac troponins and creatine kinase MB are commonly used, they may not rise during the early stages in contrast to IMA which starts elevating within few seconds of onset of ischemia. IMA having high sensitivity for the diagnosis of myocardial ischemia and high negative predictive value to rule out the patients presenting with chest pain with noncardiac cause, is an ideal marker in patients of acute coronary syndrome. Although the elevated IMA levels in non cardiac cases like ischemic stroke, diabetes mellitus and pulmonary embolism questions its specificity, it appears to offer an early test on admission combined with ECG findings and other cardiac markers for the better diagnostic efficiency. It can also be used as an independent predictor of short term and long term outcomes in patients with acute chest pain.

Keywords: Ischemia, Acute Coronary Syndrome, Troponin, Creatine Kinase MB



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Corresponding Author: DR. SHILPASREE A. S.

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INTRODUCTION

Acute coronary syndrome (ACS) includes unstable angina, ST segment elevation myocardial infarction (STEMI) and non ST segment elevation myocardial infarction (NSTEMI). Patients with ACS usually present to the emergency department with the history of acute chest pain. Distinguishing ACS from noncardiac chest pain represent a major diagnostic challenge. Usually the diagnosis of ACS is made with the typical signs and symptoms, ECG changes and with the cardiac biomarkers. The resting 12 lead ECG is the initial diagnostic tool for the assessment of such patients. Typical ECG changes helps in the diagnosis of STEMI. In patients with atypical or no ECG changes the diagnosis of NSTEMI or unstable angina is made based on the levels of cardiac biomarkers. Most commonly used cardiac markers are cardiac Troponins (Tn), Creatine kinase MB (CK MB) and Myoglobin. Even though the markers are highly sensitive for the diagnosis of myocardial necrosis, their usefulness in myocardial ischemia is limited. Since the myocardial necrosis is a time dependent process, the level of these biomarkers will be normal during ischemia and may rise after few hours only when the myocardial cell death occurs. Due to this, diagnosis of myocardial ischemia remains as a challenge in emergency medicine and there is an urgent need to identify a biochemical marker for the early detection of myocardial ischemia.¹

In the past few years, many studies have evaluated the usefulness of Ischemia modified albumin (IMA) in the diagnosis of myocardial ischemia. Human serum albumin (HSA) has N terminal aminoacid sequence aspartate- alanine- histidine- lysine that binds to the transition metal ions like copper and cobalt. This portion of HSA is less stable and susceptible to biochemical degradation. It is hypothesised and confirmed by in vitro experiments that myocardial ischemia results in the modification of N terminal end of HSA in such a way that it can no longer bind to cobalt. Resulting modified albumin is termed IMA. There are many mechanisms responsible for the generation of IMA. Ischemia causes oxidative stress and generation of oxygen free radicals like superoxide radicals and hydroxyl radicals, which modify the N terminal end of HSA. Other mechanisms being release of lactic acid as a result of localised ischemia and the release of free fatty acids as a result of hyperadrenergic state in myocardial ischemia. All these changes result in the release of cobalt from N terminal end of HSA and rise in the con of IMA. Even though there is not much evidence; IMA can also be used as a marker of oxidative stress.²

IMA is an early marker starts increasing within few min of onset of ischemia and stay elevated for 6-12 hrs in contrast to other commonly used markers like CK MB, troponins and myoglobin which starts increasing only after the myocardial cell death that is after 4 to 6 hrs. However many patients will have myocardial ischemia in the absence of myonecrosis, in such patients the markers like CK MB, troponins and myoglobin have a limited role in the confident diagnosis of ACS. Hence IMA is especially useful in the diagnosis of patients presenting immediately after

the onset of chest pain. In a study conducted by MK sinha et al in 208 patients presenting to the emergency department within 3 hrs of onset of chest pain sensitivity of IMA for the diagnosis of ACS was 82% compared with 45% of ECG and 20% of troponin T. Combination of all the three markers significantly increased the sensitivity to 95%. In the same study IMA performed better in the diagnosis of unstable angina compared to ECG. The sensitivity of IMA for the diagnosis of UA and NSTEMI was higher (91% and 69%) compared to ECG (32% and 50%). IMA also shows negative correlation with left ventricular ejection fraction in patients with UA. The levels will be significantly high in patients with abnormal LVEF (<50%) than in patients with normal LVEF (>50%). However in the identification of patients with STEMI, ECG performed better than IMA (sensitivity 95% and 60% respectively)^{3,4} Although IMA is a sensitive marker of ischemia, the sensitivity is low in cases of reversible and transient ischemia. This results in the normal IMA levels in cases of stable and variant angina.⁵

Along with the high sensitivity, IMA has high negative predictive value to rule out ACS in patients presenting with chest pain without cardiac ischemia. This helps to shift such patients to low risk category after initial evaluation of IMA.⁶ By using a cut off value of 90U/l IMA had 80% sensitivity and 92% negative predictive value. This was significantly high compared to ECG and the other markers of myonecrosis.¹ for the efficient management of Emergency department, high NPV is most critical since the identification of true negatives and accurate exclusion of ACS preserves the limited and expensive resources. Many studies have reported the high sensitivity, negative predictive value but low specificity of IMA for the diagnosis ACS either used alone or in combination with ECG or TnT.⁷

High IMA levels have been observed in transient myocardial ischemia induced by percutaneous coronary interventions (PCI). IMA can also be used as a prognostic factor during coronary artery bypass surgery. Myocardial ischemia of various degrees develops during coronary bypass surgery which results in very high intraoperative IMA levels than preoperative and post operative levels. High IMA levels correlate with the bad prognosis after coronary artery bypass surgery.^{8,9}

Estimation of IMA

Estimation of IMA is done by albumin cobalt binding assay. The assay measures the cobalt binding capacity of albumin in serum sample. The sample should be collected freshly or can be stored at 4 °C up to 2 hours for the measurement. Samples frozen at -20 °C are stable but slightly higher values are observed compared to the freshly collected samples.¹⁰ A known amount of cobalt is added to the serum sample. Cobalt will bind to the N terminal end of HSA. Dithiothreitol (DTT) is added which binds to any remaining unbound cobalt producing a colour which is measured spectrophotometrically. In serum of patients with ischemia, IMA loses its ability to bind with cobalt leaving more free cobalt to react with dithiothreitol producing a

darker colour. Hence the absorbance will be proportional to the amount of IMA in the serum sample.

Role of IMA in noncardiac ischemia.

There have been many reports showing elevated IMA levels in noncardiac ischemia cases like acute ischemic stroke, pulmonary embolism and diabetes mellitus. Many studies have reported the elevated IMA levels in transient ischemic attack and ischemic stroke patients.⁵ In a study conducted by Nayak AR et al in 5 patients with acute ischemic stroke, the level of IMA was significantly high compared to the controls. Follow up estimation of IMA levels showed significant reduction in levels on follow up till 72 hrs. This is important in the prediction of clinical status and the outcome of ischemic stroke patients.¹¹ Roy et al have reported that IMA levels decreases immediately after exercise induced leg ischemia in patients with peripheral vascular diseases. In healthy individuals, transient decrease in IMA levels have been observed immediately after skeletal muscle exercise followed by the delayed increase after 24 to 48 hrs.¹²

IMA levels will be high in patients with type2 diabetes mellitus than the healthy individuals and the levels correlate with the development of ketosis. Hyperglycaemia induced oxidative stress is responsible for the elevated IMA levels in diabetic ketosis patients. Studies have demonstrated the significant reduction in the levels followed by the insulin therapy.¹³ In patients with pulmonary embolism with or without deep vein thrombosis, IMA levels will be significantly high compared to the controls. Being highly sensitive and less expensive than the commonly used marker D dimer IMA has a great potential in the diagnosis of pulmonary embolism.¹⁴

The use of IMA can improve the current diagnostic strategy of chest pain due to its high sensitivity and negative predictive value. Since IMA is elevated during the early stages of ischemia it helps to identify the patients who develop myonecrosis later and to start effective therapy. Due to the high NPV of IMA it is possible to exclude the patients presenting with chest pain without myocardial ischemia. IMA shows significant correlation with other cardiac markers and ECG, hence it can be used in conjunction with Tn T and ECG to triage the patients who present to the emergency department with the symptoms of ACS.

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