Contents lists available at www.innovativejournal.in

INNOVATIVE JOURNAL OF MEDICAL AND HEALTH SCIENCE

Journal homepage: http://www.innovativejournal.in/index.php/ijmhs

ISSN No. 2277-4939

ROLE OF ISCHEMIA MODIFIED ALBUMIN IN THE EARLY DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

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ARTICLE INFO

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Keywords Acute myocardial infarction, Unstable angina, Ishcemia Modified albumin, Cardiac markers

ABSTRACT

The primary aim of this study was to investigate serum Ischemia Modified Albumin (IMA) as a useful marker in the early diagnosis of Acute myocardial infarction (AMI). A total of 144 patients admitted in the Intensive care unit of PSG Hospitals with suspected AMI and 73 healthy control subjects were enrolled in this observational study. 24 patients were excluded. Serum cTnT was estimated by a fully automated Immunodiagnostics analyzer ROCHE Elecsys 2010. IMA was estimated by a spectrophotometric method as described by Bar Or et al. The diagnostic sensitivity of the two markers were analysed using students 't' test. Patients were divided into the AMI group (n = 104), the unstable angina group (n=10) and the non-ischemic chest pain group (n = 06), according to the ECG results. Mean IMA values were higher in AMI group ($p < 0.00001$) and in patients with Unstable Angina (UA) ($p < 0.005$) compared with control. The diagnostic sensitivity of IMA was higher than cTnT in STEMI (100% vs 68%), NSTEMI (97% vs 44%) and in unstable angina(100% vs 0%) . In UA the cTnT levels remained below the cutoff level (<0.03 ng/mL). The increase in IMA levels was noted within minutes after the onset of symptoms and remained elevated after 6 hrs. The cTnT levels were below the cutoff levels in UA, whereas the IMA levels are elevated significantly ($p < 0.005$) compared to controls.We have shown that IMA is a potential diagnostic biomarker for UA than cTnT and assessment of serum IMA in patients with chest pain will improve current diagnostic strategies for acute chest pain patients to avoid adverse cardiac events.

INTRODUCTION

Myocardial Ischemia results due to inadequate blood perfusion to myocytes leading to a deficiency of oxygen and nutrients, eventually compromising their vital function. Prolonged ischemia can lead to myocardial cell death known as Acute Myocardial Infarction (AMI). [1] Ideally we should be able to identify myocardial ischemia before it progresses to the irreparable myocardial cell damage. Heart disease has been the leading cause of death in the United States since the previous century and also results in substantial health-care expenditures; Myocardial Ischemic manifestations are vague and multiple[2-5]. However, these symptoms are subtle and are not easily recognized. Because of the varied presentation and associated high mortality, the early identification of patients with AMI is very critical for the patient management and has a bearing on the prognosis. Biochemically, AMI is diagnosed with the help of myocardial proteins in the serum viz. Troponins (T & I) along with ECG and other modalities. These Cardiac markers of cell necrosis are highly sensitive and exhibits good specificity. They do not however, detect myocardial ischemia in the absence of necrosis and provide no reliable information when measured in the first 2-6 hours following an ischemic event.[6,7] Thus identification of a rapidly measurable biochemical marker that is sensitive and specific for myocardial ischemia is of great importance.

The amino terminus end (N terminal) of the albumin is the binding site for transition metals such as cobalt, copper and Nickel.[8] During ischemia N-terminus of albumin is altered, known as Ischemia Modified Albumin (IMA), possibly as the result of hypoxia, acidosis, free radical

injury, Na and Ca pump disruptions. [9] This results in lowering of its binding capacity for metals.[10,11] So assessment of binding capacity of serum albumin with exogenous cobalt will help in the diagnosis of Acute Myocardial Ischemia[12,13].

This assay is reported to be positive within 6-10 min of ischemia and remains so until up to 6 hours later, allowing detection before the development of necrosis as evidenced by normal levels of CK-MB, Troponin and myoglobin.[14,15] Regarding IMA clearance, the changes to albumin may not be irreversible. Thus, the rapid return to normal within a few hours (12-24) may be a function of return to pre ischemic conditions with the removal of the free radicals, or an accelerated clearance due to a conformational change to the protein.[14, 15]

The present study was thus undertaken to assess the clinical utility of IMA Assay in Acute myocardial infarction (AMI).

MATERIALS AND METHODS:

The Study was conducted at Department of Biochemistry, PSG Institute of Medical Sciences and Research after obtaining the approval by the Institutional Human ethics committee. A total of 144 patients of either sex with suspected AMI and 73 age matched healthy control participants were enrolled in the study. 24 patients were excluded because of predefined criteria: Renal failure (n=11), Cerebro-vascular accidents (n=5), COPD (n=4), Sepsis (n=3), Peripheral Vascular Disease (n=1). All the suspected AMI patients underwent ECG at the time of admission. Blood samples were collected from the above subjects using BD vacutainers with silica as the clot activator. Serum Cardiac Troponin T was estimated by fully automated Immunodiagnostics analyzer ROCHE Elecsys 2010 using dedicated kit and IMA was estimated by a spectrophotometric method as described by Bar Or et al.[16]Values are expressed as Mean ± SD. Results were analyzed using students T test.

RESULTS:

The mean age of the suspected AMI group was 58±13.5 (Range-35-80y) and the control group was 55±16 (range-35-80y). 75% of the both experimental and control group were males.

Based on the ECG findings patients were divided into three groups, the AMI group (n = 104), the unstable angina group (n=10) and the non-ischemic chest pain group (n = 06), according to the ECG results. Our diagnostic work-up is presented in Figure 1. In the present study it was observed that the mean IMA values were higher in AMI group (p <0.00001) as well as in patients with UA (p <0.005) compared with control (fig-2). However the cTnT levels of unstable angina (0.011±0.006ng/mL)patients did not differ significantly with the controls (<0.01ng/mL) even though the AMI patients (0.8157±2.119ng/mL)showed a significant elevation (<0.0005). The sensitivity percentage of IMA, ECG & cTnT used alone and in combination for diagnosis of ACS including AMI & UA are presented in Fig 3. The diagnostic sensitivity of IMA for ACS was found to be is highest followed by ECG & cTnT. Estimating serum IMA along with both serum cTnT and ECG significantly elevated the diagnostic sensitivity in AMI as well as UA patients.

It was also observed that the diagnostic sensitivity of IMA was higher than cTnT in STEMI (100% vs 68%), NSTEMI (97% vs 44%) and in unstable angina(100% vs 0%) . The unstable angina patients the cTnT levels remained below the cutoff level (<0.03 ng/mL).

In addition IMA elevation was found to be immediate after the onset of chest pain where as cTnT showed a delayed rise as shown in Fig 4. The increase in IMA levels was noted within minutes after the onset of symptoms and remained elevated after 6 hrs. It was also observed that the IMA levels in unstable angina patients were elevated significantly (p <0.005) compared to controls where as cTnT levels were below the cutoff levels (Table-1).

DISCUSSION:

A biomarker of ischemia such as IMA may improve our ability to identify ischaemic patients who are missed by current diagnostic strategies, or more confidently rule out patients who do not have ACS. More than 50% of patients presenting to the emergency deprtment (ED) with chest pain are admitted to a hospital to rule in or rule out ischemic heart disease (IHD).[17,18]An underlying cardiac origin of the pain is ultimately ruled out in about half of admitted patients. For efficient management in an ED, Non Predictive Value (NPV) may be most critical. False negatives are an undesirable outcome but true negatives are of greater importance because the accurate exclusion of ACS preserves limited and expensive resources.[19] High sensitivity will drive high NPV in a low prevalence population because of the comparatively smaller number of false negatives.

The study population was defined as AMI & UA (ACS) based on the ECG findings and final diagnosis. This study showed that the sensitivity of IMA for the diagnosis of acute ischemic chest pain is significantly greater than that of cTnT. UA with normal cTnT (cut off = 0.03 ng/ml) accounted for 8.3% of the positive ACS diagnoses in this study, identification by IMA was 100%. Our findings confirm and expand upon previous report that in a human model of ischemia induced by balloon angioplasty, IMA rises early after balloon inflation and levels returns to baseline within 6-12 hours.[15,16]

Conventional ED testing in patients presenting with chest pain includes ECG and cTn T. In this study, the presentation ECG combined with cTnT identified 44.2% of patients with a discharge diagnosis of UA, NSTEMI, or STEMI. When IMA was added to either the ECG or cTn T measurements, or both, the sensitivity for diagnosis increased to 97.5%. Thus the addition of IMA to current standard tests may identify additional patients with IHD

who could benefit from earlier treatment or more confidently rule out patients without IHD. In the present study the diagnostic sensitivity of serum IMA levels was higher than cTnT. cTnT diagnostic sensitivity improved after 6h indicating myocardial necrosis.

The levels of serum IMA are significantly ($p<0.005$) higher in patients with unstable angina (0.529 ABSU) compared to control subjects (0.36ABSU).

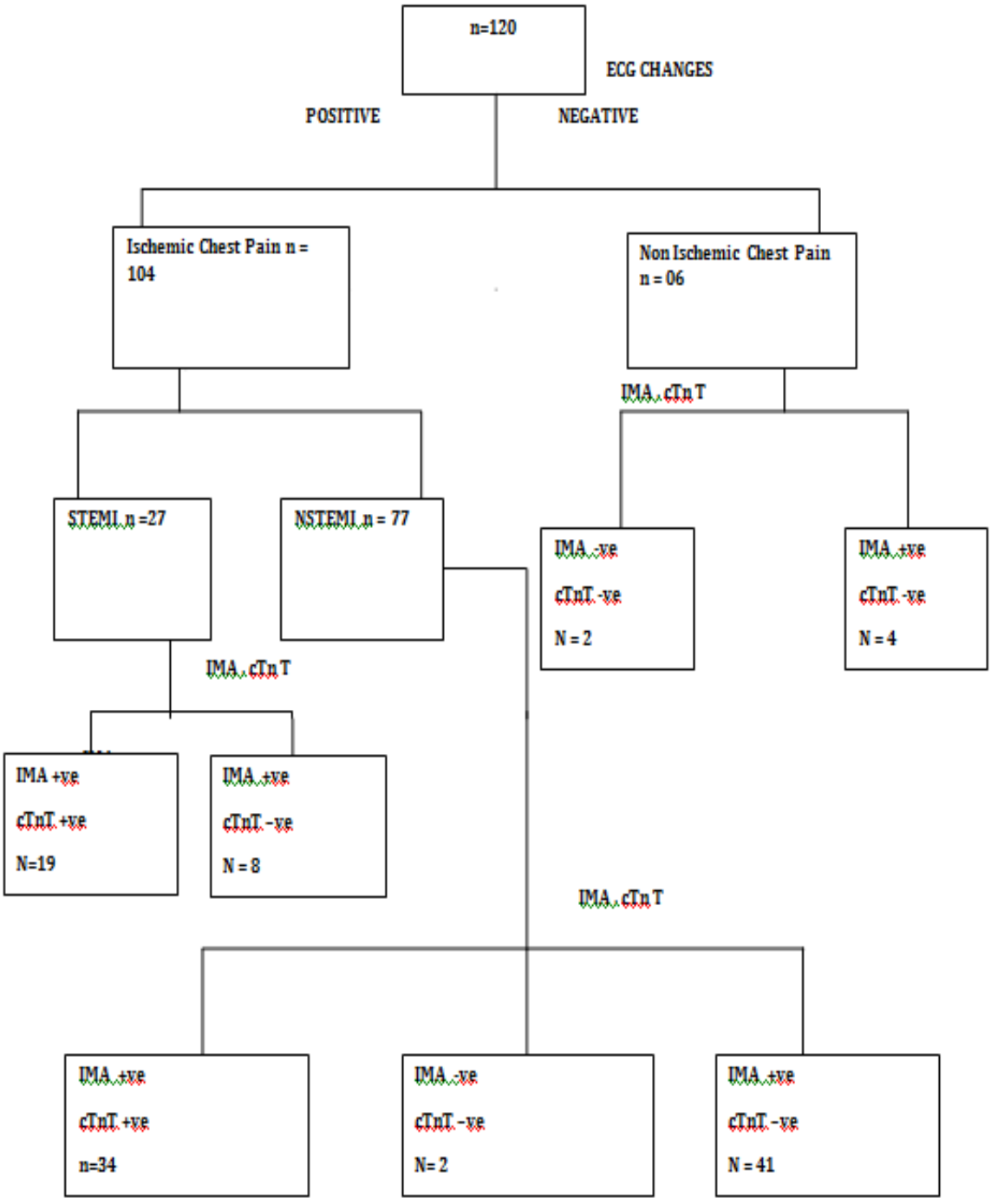

FIG: 1

CTnT levels of UA patients did not rise from the base line values (0.03ng/mL) indicating serum IMA as a better marker for the diagnosis of MI before necrosis. Blood levels of IMA rise promptly during myocardial ischemia triggered by a primary reduction of blood flow (supply ischemia), as seen in patients undergoing percutaneous coronary intervention (PCI), stay elevated for about 6 hours and return to baseline within 12 hours.[20-22] In a previous report, IMA production was decreased in patients with collateral vessels, which is likely to be a protective effect of collateral circulation against PCI-induced myocardial ischemia-reperfusion injury.[21]

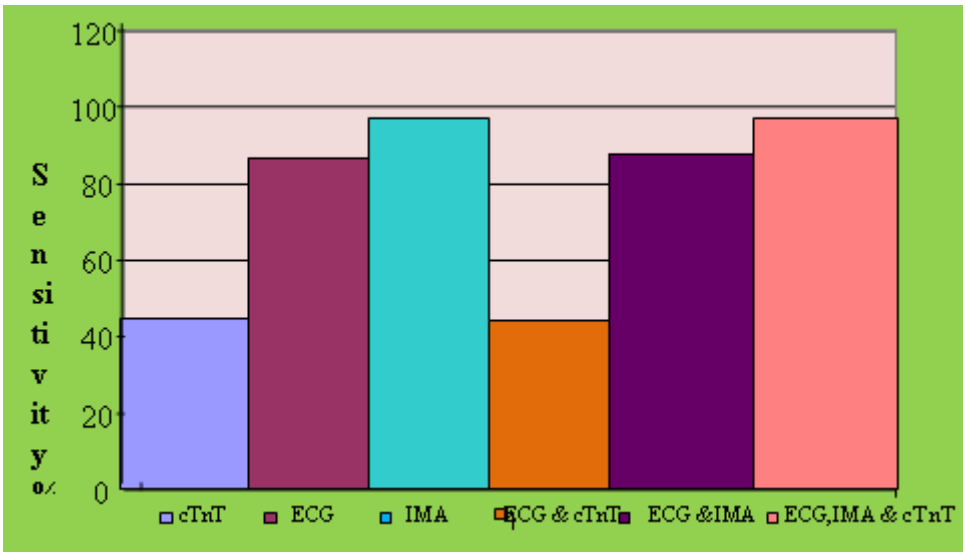

FIGURE 2: MEAN IMA LEVELS IN CONTROL, AMI & UA GROUPS

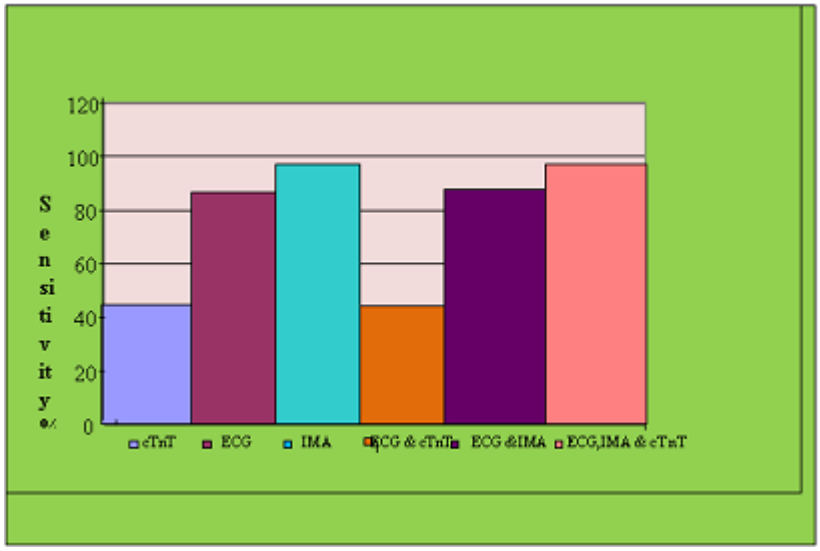

Figure 3: Comparative sensitivities for diagnosis of ACS including AMI & UA

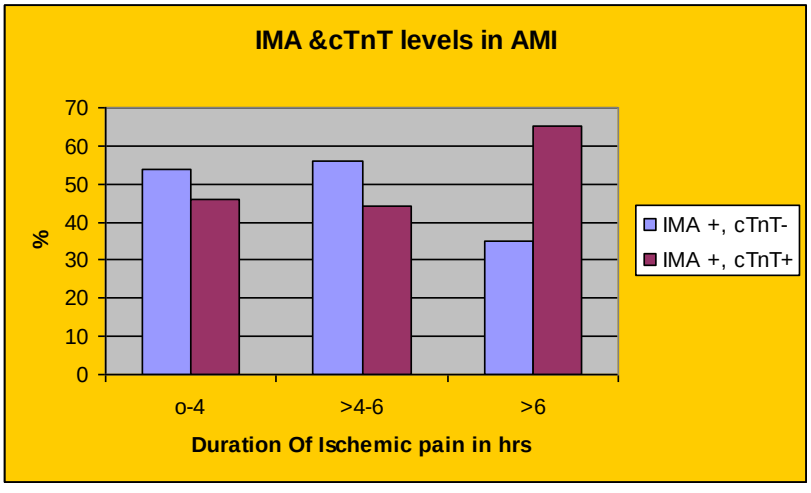

Figure 4: IMA and cTnT levels in AMI

Table I: SERUM IMA & cTnT LEVELS IN UNSTABLE ANGINA PATIENTS

	N	IMA		cTnT	
		ABSU	p	ng/mL	p
Control	12	0.36±0.0162		<0.01	
UA	10	0.529±0.144	<0.005		**NS**

IMA : Ischemia Modified Albumin
cTnT : Cardiac Troponin T

At present there is no gold standard for myocardial ischemia and this is one of the main challenges faced in the testing of a marker such as IMA. In our study IMA results were compared with the final "hospital" diagnosis, which represented the "gold standard" [23]for the purpose of the study. Final hospital diagnosis resulted from the analysis of all available clinical data-that is, the clinical history, ECG, exercise ECG, perfusion scans, stress echo-cardiography & coronary angiography.

In this selected population our aim was to objectively assess the ability of IMA to detect ACS. In our study elevated serum IMA levels was observed in 67% of NICP group who were diagnosed for non cardiac problems as per the previous strategy. The observed increase in these patients may be related to ischemia in any other organs. It is possible that increases in IMA could, in theory be observed during ischemia affecting any organ. Increased concentrations of IMA have been demonstrated 24-48 hours after endurance exercise and it has been hypothesized this is related to delayed gastrointestinal or skeletal muscle ischemia. [22]

This study shows that IMA has high sensitivity for prediction of a discharge diagnosis of ACS, but comparatively low specificity (in contrast with presentation troponin, which has high specificity but very low sensitivity). One of the reasons for this may well be that IMA is detecting ischemia that is subclinical and beyond the ability of conventional diagnostic methods to identify.

In this study, there was a significant, albeit comparatively small difference in IMA values when patients with NICP and those with UA were compared. This may be accounted for by selection bias as the patients included in the study were highly likely to have ACS.

In two of the NSTEMI subjects the serum IMA levels was lower than that of the control. In myocardial necrosis fewer albumins will be exposed to circulating free radicals resulting in lesser IMA production. Because of the difficulty of pinpointing the exact time of onset of an ischemic event, there is always the possibility that IMA was initially raised but had already decreased below the diagnostic cut off at the time of the blood draw. These intriguing findings do not detract from the fact that IMA is a sensitive marker of ischemia (rather than necrosis). From a practical clinical perspective, AMI is often an unequivocal diagnosis indicating the urgent need for thrombolytic therapy or coronary intervention and IMA testing may be more clinically relevant in these settings.

We have shown that IMA has potential as a diagnostic biomarker for UA. Significantly more UA patients were recognised at presentation by IMA than by cTnT. . If the present results are confirmed by additional studies, the use of IMA may improve current diagnostic strategies for acute chest pain patients to avoid adverse cardiac events.

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