Ischemia Modified Albumin – An Early Marker of Myocardial Ischemia

Authors
Dr R.Panimathi* M.D (Bio), D.CH1, Dr Lalitha M.D2

1 Associate Professor of Biochemistry, Govt Thiruvarur Medical College, Thiruvarur, Tamilnadu, India
Email: panimathi@hotmail.com, Contact No: 9443401760

2Prof & Head of Dept (Retd), Govt Kilpauk Medical College, Kilpauk, Chennai

ABSTRACT
Introduction: Coronary heart disease (ischemic heart disease-IHD) is projected to be the leading cause of death by 2030, accounting for 25-30% of deaths in industrialized countries.

Aim and objective: To estimate serum Ischemia Modified albumin in myocardial ischemia patients and to correlate it with Ck-MB and lipid profile.

Materials and Methods: The present study was conducted to estimate serum Ischemia modified albumin by Albumin Cobalt Binding Assay in fifty subjects who were admitted in the Intensive Coronary Care Unit with complaints of chest pain of less than 6 hours duration along with ECG showing S-T,T changes. This was compared with fifty healthy subjects.

Results and Observation: Statistical analysis in the study group showed the mean value of Ischemia modified albumin as 88.52 IU/ml and sensitivity of 78% which revealed a significant raise than Ck-MB [mean value of 56.50 U/Land sensitivity of 69%] during the early hours of ischemia. With an area under the curve of 0.921 and a standard error of 0.028, it also showed an asymptomatic significance of 0.001 proving it as a better predictor over Ck-MB in diagnosing myocardial ischemia.

Conclusion: Values obtained suggested a significant correlation between ischemia modified albumin and CK-MB,and also with age, total cholesterol and low density lipo protein. Analysis of Ischemia modified albumin helps to diagnose myocardial ischemia at an Earlier stage in the first 2-6 hours following an ischemic event before it progresses to irreversible myocardial cell damage and necrosis, unlike other previous laboratory parameters that identify myocardial damage only after it is well established

Keywords: IHD-ischemic heart disease, ACS-Acute coronary syndrome, IMA-ischemia modified albumin,
40 to 60 years but also occurs earlier when other 
risk factors co-exist2. Males are more affected by 
IHD than females. Clinical IHD in pre-menopausal women is very low due to estrogenic 
effects. The familial predisposition to 
atherosclerosis and Coronary Heart Disease is 
polygenic. Type Abehaviour doubles the risk of 
Coronary Heart Disease in otherwise healthy men. 
Under modifiable risk factors Hypertension 
accelerates the atherosclerotic process especially 
if hyper lipemia is also present. The degree of 
risk of developing CHD is related to the number 
of cigarettes smoked per day. Smoking 
accelerates atherosclerosis and promotes acute 
ischemic events3.Greater the weight gain greater is 
the risk of hyper tension, CHD and insulin 
resistance diabetes mellitus. Presence of hyper 
cholesterolemia is sufficient to initiate the disease 
process by inducing an endothelial injury in the 
coronary arteries. Serum cholesterol 
concentration associated with low density 
lipoprotein which serves as a vehicle for the 
delivery of cholesterol to peripheral tissues play a 
major role in precipitating CHD3.CHD is 2-3 
times higher in diabetics than in non-diabetics. 
Sedentary life style with reduced physical activity 
leads to an early development of CHD. High 
alcohol intake defined as 75g or more per day 
becomes an independent risk factor for CHD 3.

Clinical types of IHD
Patients with IHD fall into two large groups.
1) Patients with chronic coronary artery 
disease.
2) Acute coronary syndromes.

Chronic coronary artery disease:
These patients commonly present with ANGINA 
PECTORIS where the ischemia causes pain but is 
insufficient to lead to death of myocardium. 
Acute coronary syndrome (acs) - 
Acute Coronary Syndrome comprises of a 
spectrum of disease that encompasses ischemia 
with minimal myocardial damage (i.e.) unstable 
angina and Myocardial Infarction. This infarction 
may be

1) STEMI – (ST elevation myocardial 
infarction)
2) NSTEMI – (Non ST elevation myocardial 
infarction) 4.

Pathogenesis of atherosclerosis:-
Atherosclerosis is a complex disease that involves 
lipoprotein influx and modification, increased 
prooxidant stress and inflammatory angiogenic 
and fibro proliferative responses intermingled 
with extra cellular matrix and smooth muscle cell 
proliferation resulting in the formation of 
atherosclerotic plaque 5.

Acute changes of plaque:-
The initiating events that disrupts a plaque are 
1) Rupture, fissuring or ulceration of plaques 
exposing highly thrombosed plaque 
constituents or underlying sub endothelial 
basement membrane.
2) Hemorrhage into the core of plaques with 
expansion of plaque volume and 
worsening of the limited occlusion 6.

Role of thrombus:-
Rupture of plaques fibrous cap causes thrombosis 
that leads to episodes of unstable angina 6.

Patho physiology of IHD :-
The extent of damage to myocardium and the 
irreversibility of the ischemic cardiac muscle 
depend on  
1) The metabolic needs of the under perfused 
tissue.
2) Degree of existing collateral vessels.
3) Location, severity, duration and rate of 
development of arterial occlusion7.

ISCHEMIA MODIFIED ALBUMIN
In ischemia of the myocardium, within seconds of 
vascular obstruction, aerobic glycolysis ceases in 
the myocytes, leading to inadequate production of 
adenosine triphosphate and depletion of creatine 
phosphate resulting in the accumulation of lactic 
acid, NADH and fall in pH 3.Reduced pHleads to 
release of bound copper and iron from protein and 
intracellular stores. Ischemia also reduces the 
electron carriers, thereby leading to the formation 
of reactive oxygen species like super oxide anions 
8.
These free radicals oxidatively damage the histidine present in the amino terminal region of albumin. This albumin which has a damaged amino terminal is called Ischemia Modified Albumin (IMA)\(^9,10\).

Normal albumin has a binding affinity for transitional metals like cobalt at its amino terminal. But Ischemia Modified Albumin lacks its ability to bind to cobalt which forms the basis for Albumin cobalt binding assay in measuring Ischemia Modified Albumin in myocardial ischemia\(^11\). IMA starts increasing within 6 to 10 minutes of ischemia, reaches a peak by 4 hrs and returns to baseline after 6 hrs in transient ischemic conditions, like after Percutaneous transluminal angioplasty. Whereas the N-Terminal oxidative damage to albumin is cumulative and the repair is slow in cardiac ischemia, and the level also will not raise after 6 hours\(^12,13\).

**AIM OF THE STUDY**

Aim of the study is to measure the Ischemia Modified Albumin by Albumin Cobalt Binding assay in patients, within 6 hours of onset of chest pain.

**Objective**

1) To correlate the IMA values with CK-MB
2) Correlation of other markers of atherosclerosis like
   (a) Total cholesterol
   (b) Triacylglycerol
   (c) High density lipoprotein
   (d) Low density lipoprotein
   (e) Very low density lipoprotein with IMA
3) To prove the use of IMA as an early marker of myocardial ischemia.

**MATERIALS AND METHODS**

The study was conducted after getting the approval from the ethical committee of Stanley Medical College. Hundred subjects were chosen for the study. Both males and females in the age group of 30-70 years were included and an informed consent was obtained from all of them.

Fifty subjects with normal, clinical, biochemical parameters and with normal ECG served as the control group. They were selected from the master health checkup outpatient department of Stanley Medical College.

Fifty subjects who were admitted in Intensive coronary care unit [ICCU] with complaints of chest pain (of < 6 hours duration), with Electrocardiographic findings showing ST changes formed the study group and they were selected from the department of cardiology, Stanley Medical College.

**INCLUSION CRITERIA**

1) Patients admitted with complaint of chest pain within 6 hours of onset.
2) Electrocardiographic findings showing abnormal ST-T wave changes (ST segment elevation or depression or deep symmetrical T wave inversion).

**EXCLUSION CRITERIA**

1) Presence of renal diseases.
2) Presence of cirrhosis.
3) Presence of stroke, skeletal muscle injury, malignancy, trauma.
4) Critically ill patients.
5) Ongoing infectious diseases.
6) Serum albumin < 2 gms/dl, Serum creatinine> 3 mgs/dl.

**BLOOD COLLECTION**

5ml of blood samples were collected by venipuncture with strict aseptic precaution as soon as the subjects got admitted as per the inclusion criteria.

The samples were centrifuged and serum separated. One part of the sample was taken and analysis of CK-MB, albumin and creatinine were done immediately. Remaining part of the sample was stored for analysis of Ischemia Modified Albumin at 20\(^\circ\)C.

12-14 hours fasting sample was also collected from all subjects during their hospital stay and analysis of total cholesterol, triacylglycerol and high density lipoprotein were done.

Lab methods:
Ischemia modified albumin was estimated by chemical method using albumin –cobalt binding assay. Rests of all analytes were analyzed by ERBA-Transasia kit using Cobas Mira auto analyzer.

RESULTS AND STATISTICAL ANALYSIS
A total of 100 patients were included in the present study. Out of the 100, 50 were study group [IHD patients within 6 hours of onset of Chest pain] and other 50 were controls [Normal individuals].

AGE DISTRIBUTION AMONG THE STUDY AND CONTROL GROUP:-
Male and Female patients in the age group of 35 years to 70 years were taken in the study. Both the study and control group were age matched. The mean age of the control group is 51.48 and the mean age of the study group is 52.04.

TABLE – 1

| Group  | N  | Minimum age | Maximum age | Mean | Standard Deviation | Student independent ‘t’ test |
|--------|----|-------------|-------------|------|--------------------|----------------------------|
| Control| 50 | 35          | 67          | 51.48| 8.853              | P=0.09                     |
| Study  | 50 | 35          | 68          | 52.04| 9.178              | Not Significant            |

The serum levels of IMA & CK-MB total cholesterol, Triacylglycerol and High density lipoprotein were estimated for all the patients taken for the study. Very low density lipoprotein and low density lipoprotein values were calculated. Mean and standard deviation were calculated for the quantitative variables, Total cholesterol, Triacylglycerol, High density lipoprotein, very low density lipoprotein and low density lipoprotein, IMA & CK-MB, in both study and control group. The values were analysed and the results are presented in table-2

Correlation between IMA and Ck-MB were analyzed using pearson’s correlation analysis. The results are presented in table 3.

The Receiver operating characteristic [ROC] Curves are plotted for IMA and CK-MB and presented in figures I .and II

COMPARISON OF BIOCHEMICAL PARAMETERS IN THE STUDY AND CONTROL GROUP

TABLE – 2

| Parameter                        | Group  | Mean   | Standard deviation | ‘P’ value |
|----------------------------------|--------|--------|--------------------|-----------|
| IMA                              | Control| 38.35  | 13.95              | P=0.001   |
|                                  | Study  | 88.52  | 26.57              | Significant |
| CK-MB                            | Control| 12.32  | 4.23               | P=0.032   |
|                                  | Study  | 56.50  | 49.21              | Significant |
| Total Cholesterol                | Control| 166.12 | 17.67              | P=0.04    |
|                                  | Study  | 208.44 | 37.29              | Significant |
| Triacyl glycerol                 | Control| 125.45 | 24.25              | P=0.058   |
|                                  | Study  | 128.38 | 16.94              | Significant |
| High density lipoprotein         | Control| 44.04  | 9.53               | P=0.01    |
|                                  | Study  | 34.44  | 8.43               | Significant |
| Low density lipoprotein          | Control| 96.00  | 22.64              | P=0.032   |
|                                  | Study  | 148.26 | 35.18              | Significant |
| Very low density lipoprotein     | Control| 24.96  | 4.91               | P=0.05    |
|                                  | Study  | 25.70  | 3.40               | Significant |
PEARSON’S CORRELATION ANALYSIS IMA WITH OTHER VARIABLES

TABLE – 3

| IMA      | Age  | CK-MB | TC   | TAG  | HDL  | LDL  | VLDL |
|----------|------|-------|------|------|------|------|------|
| Correlation 1 | 0.132 | 0.53  | 0.482 | 0.062 | 0.374 | 0.55  | 0.459 |
| Significance [2 tailed] | 0.031 | <0.001 | 0.004 | 0.06  | 0.001 | 0.002 | 0.56  |

Figure I
RECEIVER OPERATING CHARACTERISTIC CURVE FOR ISCHEMIA MODIFIED ALBUMIN (IMA) and CK-MB

![ROC Curve]

DIAGONAL SEGMENTS ARE PRODUCED BY TIES
DISCUSSION
The present study establishes the characterization of the IMA test for its association in the early diagnosis of Myocardial Ischemic patients and its comparison with CK-MB, the common biochemical marker of Coronary Heart Disease. In the present study, the mean value of IMA of 88.52 units/ml in the study group showed a significant rise than CK-MB during the early hours of ischemia with a sensitivity of 78%. This study also correlates with the data given in previous studies on Ischemia Modified Albumin- as a novel marker of Acute Coronary Syndrome\textsuperscript{14}. 

**Figure II**

DIAGONAL SEGMENTS ARE PRODUCED BY TIES
IMA / CK-MB LEVELS WITH DURATION OF CHEST PAIN

BAR DIAGRAM FIGURE - 1
Various epidemiological and clinical studies have shown strong relationship between IMA and CK-MB levels increase in relationship to duration of chest pain $^{15}$. The present study also shows a strong positive correlation with duration of chest pain which is depicted in the bar diagram in (Fig-1). There is significant serial elevation in IMA levels from 2 hours to 6 hours of onset of chest pain compared to the percent increase in CK-MB levels. ROC curve of IMA and CK-MB reveal that the IMA curve is above the assay curve of CK-MB $^{16}$.

AREA UNDER THE CURVE
Test result variable (IMA)

| Area    | Std error | Asym sig | Asymptomatic confidence interval |
|---------|-----------|----------|---------------------------------|
| 0.921   | 0.28      | 0.000    | Low bound: 0.866 | Upper bound: 0.976 |

With an area under the curve of 0.921 and a standard error of 0.028, IMA showed an asymptomatic significance of 0.000 proving it as a better predictor over CK-MB, in diagnosing myocardial ischemia. Hence IMA is a better assay for evaluating ischemia before CK-MB.

When the mean values of IMA and CK-MB are compared in the study and control groups, a significant relationship exists between both the study and control groups in all age group especially in the age group of < 40 years, 41-50 years and > 60 years Comparing the presence of
risk factors, myocardial ischemia in <40 years can be attributed to smoking and alcohol consumption in this age group. Onset of HT and Diabetes in addition, contributed to the precipitation of myocardial ischemia in patients over the age group of 40 years. In the Pearson’s correlation analysis, there is a significant correlation noticed between IMA and CK-MB with age, Total cholesterol and LDL. Progressive atherosclerosis with increasing age leads to ischemia with super added risk factors precipitating the development of atherosclerosis at an early age. Alteration in food habits and life style changes can decrease the effects of modifiable risk factors over atherosclerosis which can delay the onset of ischemia.

LIMITATIONS OF THE STUDY
1) Albumin Cobalt binding (ACB) assay which is utilized to estimate IMA levels in ischemic patients is based on the modification in the amino terminal region of albumin produced by extra cellular hypoxia, acidosis, and a free radical injury disruption. Therefore ischemia in the absence of necrosis may cause bias towards apparent false positive Albumin Cobalt binding data.
2) The currently used colorimetric Albumin Cobalt binding assay is an indirect measurement of IMA production. New assay platforms (Immuno assays) are expected to be available in future which may improve the specificity of IMA.
3) Currently no reference standard exists for cardiac ischemia. A combination test of IMA with CK-MB and Troponin I can increase the sensitivity in the early diagnosis of Acute Coronary Syndrome.

CONCLUSION
Biochemical markers such as CK-MB, Cardiac Troponin-I and Myoglobin are suitable only for assessing myocardial infarction. The results of the present study confirm the findings of previous studies, that reported that the Albumin Cobalt colorimetric assay distinguishes myocardial ischemic patients from non-ischemic patients (p<0.001) Introduction of IMA assay for the first time provides emergency physicians with an objective diagnostic study to determine the presence of myocardial ischemia completely within the control of the emergency department.
IMA assay presents a quantitative accurate laboratory determination of the occurrence of an Ischemic myocardial event, Angina of various types. Unlike the previous laboratory parameters that identify myocardial damage, only after it is well established, this test (Albumin Cobalt binding assay) helps to determine which patients will go in for severe occlusion. The introduction of IMA is a welcome event and based on the results obtained, the present study supports the hypothesis that Ischemia Modified Albumin is a useful marker for the early diagnosis of myocardial ischemia before any significant increase in CK-MB levels.

BIBLIOGRAPHY
1. WORLD HEALTH ORGANISATION 1982, Technical report, ser.no. 678.
2. Douglas pZIPES, Global trends in cardiovascular disease, Braunwald’s Heart Disease, 8th Edition, Edited by; Peter libby, saunder’s publishers, page14.
3. Woolf, cardio vascular system; Atherosclerosis II, PATHOLOGY Basic and systemic, by NevilleWoolf, WB Saunders Company Ltd. Page 337.
4. Frans- J. Vandewerf, Clinical Cardiology, TEXTBOOK OF CARDIOVASCULAR MEDICINE, 3RD Edition, edited by Eric. J.Topol et-al; Lippincott Williams & Wilkins publishers, page 252.
5. Lehninger: Biosynthesis of cholesterol, steroids, and isoprenoids, PRINCIPLES
OF BIOCHEMISTRY by Lehinger 4th edition, CBS publishers, page 827.
6. Frederick J. Schoen, The Heart, ROBBIN’S BASIC PATHOLOGY, 8TH Edition, Edited by Vinaykumar et-al; Saunder / Elsevier publishers, page 390.
7. Peter G. Isaacson, Circulatory Disorders, Oxford Textbook Of Pathology vol- I, Edited by James odMc Gee, Oxford University press, page 526.
8. Frederick.j.schoen,Ramzi.s.cotran, Blood vessels, Robbins, Basic Pathology, 8TH edition, Edited by Vinaykumar et-al; saunder's Elsevier publishers. Page 344.
9. S. S. Talwalker et-al; Ischemia modified Albumin, a marker of Acute Ischemic events, A pilot study, Annals Of Clinical And Laboratory Science, Jan 1, 2008; 38(2): 132-137.
10. L. Keating et-al; The prima study: Presentation ischemia modified albumin in the emergency department, EMERGENCY MEDICAL JOURNAL, Oct 1, 2006; 23(10): 764-768.
11. D. A. Morrow et-al; The search for a Biomarker of Cardiac ischemia, Clinical Chemistry, April 1, 2003; 49(4) 537-539.
12. Gary J Fagan, Albumin Cobalt Binding Test; Analytical performance of a new automated chemistry assay for the detection of IMA, JOURNAL OF CLINICAL LIGAND ASSAY, 2002; 25: vol 25, number 2, 178-187.
13. Acute Coronary Syndrome, INTERPRETATION OF DIAGNOSTIC TESTS BY Jacques Wallach, 8th edition, Lippincott, page 129.
14. Robert H Christenson et-al; Characteristics of an ACB Test for assessment of Acute Coronary Syndrome patients; Clinical Chemistry – 47:3 464- 470 (2001).
15. Chawla et-al; Ischemia Modified Albumin: A novel marker for Acute Coronary Syndrome, INDIAN JOURNAL OF CLINICAL BIOCHEMISTRY, 2006, 21 (1) 77-82.
16. Gaze DC et-al; IMA is a sensitive marker of myocardial ischemia after percutaneous coronary intervention, CIRCULATION, 2003, MAY; 107(19):2403-5.
17. Manas.k.Sinha et-al; Markers of myocardial ischemia EUROPEAN HEART JOURNAL; oxford journal, 2006, 27(6):758
18. G.Lippi, et-al; predicting Cardiac outcomes, CANADIAN MEDICAL ASSOCIATION JOURNAL, NOV 2005; 173(10) 1206-1207.
19. Guliyian et-al; Assay of IMA, & CRP for early diagnosis of ACS, CLINICAL LABORATORY ANALYSIS, 2008; 22; 45-47.