Ischaemia Modified Albumin as a New Biomarker in the Early Diagnosis of Acute Coronary Syndrome

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Abstract

Background: Early identification of acute coronary syndrome (ACS) is important. CK-MB and cardiac troponins show a delayed rise approximately 3 to 6 hours after the onset of pain. Ischaemia modified albumin (IMA) has been licensed through FDA for the early diagnosis of myocardial ischaemia. This study aimed to assess the role of IMA in the early diagnosis of ACS.

Methods: This study was conducted on 60 patients who were admitted in the Cardiac Care Unit (CCU) of Benha University Hospitals with acute chest pain less than 3 hours before admission. All patients underwent serial IMA and cardiac troponin T (cTnT) both at presentation and after 8 hours. Patients were divided into two groups according to the discharge diagnosis: non-ischaemic or ischaemic chest pain group. This classification based on criteria of pain, ECG changes, and wall motion abnormalities by echocardiography plus positive cTnT. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) for both IMA and cTnT were analyzed.

Results: Using 75 ng/dl as a cut off value for IMA and 0.04 ng/dl for cTnT, the sensitivity and NPV of IMA to rule out ischaemia was greater as compared to that of cTnT (70.6% & 63% vs 44.1% & 42.2%). The combination between the IMA and the cTnT results improved the sensitivity and NPV up to 85.3% at presentation and up to 100% 8 hours after admission.

Conclusion: IMA is a useful marker for the early rule out of ACS. Negative IMA (<75 ng/dl) and cTnT (<0.04 ng/dl) values plus normal or non-specific ECG changes could safely rule out the ischaemic etiology of chest pain early after presentation.

Keywords
Acute coronary syndromes; Ischaemia modified albumin and cardiac troponins

Introduction

Patients with chest pain represent a very large proportion of all acute medical hospitalizations in the world. Distinguishing those with acute coronary syndrome (ACS) within the patients with chest pain represents a diagnostic challenge. Among those, coronary artery disease (CAD) is the most prevalent manifestation and is associated with high mortality and morbidity [1]. The admission ECG fails to identify many of the patients who experience cardiac event during the early follow-up periods [2]. Assessment of the cardiac biomarker levels (Myoglobin, Creatine Kinase-MB and Troponins) is one of the most essential and effective ways for detecting myocardial damage. The current conventional cardiac markers, CK-MB, Troponin I (TnI) and T are sensitive and specific tests for the detection of myocardial necrosis, but they show a delayed rise approximately 3-6 hours after the onset of the myocardial cell injury and thus, the patients may wait before they are diagnosed and treated; moreover, the usual biomarkers may not rise during reversible myocardial ischemia and other diagnostic tools such as stress testing, and echocardiography are not routinely available [3]. Hence, there is a need for a marker that can possibly overcome these limitations. Ischaemia-modified albumin (IMA) has higher sensitivity than Troponins, CK-MB and myoglobin during the early phase of ACS, and can be an ideal marker in the early diagnosis of ACS. It is hypothesized that reactive oxygen species like superoxide and hydroxyl radicals generated during ischaemia-reperfusion modify the N-terminus of human serum albumin (HSA), especially at the N-Asp-Ala-His-Lys sequence resulting in IMA formation with albumin acting as a “sacrificial” antioxidant to reduce the injury during reperfusion [4].

The compensatory hyper adrenergic state during myocardial ischemia causes the rise in plasma concentrations of free fatty acids (FFA) and the corresponding FFA-induced conformational perturbations of HSA form the basis of the IMA test. The increased lactate level in post-ischaemic state causes interference in IMA measurement and is another factor attributed to the rise in IMA. Serum levels of IMA get significantly elevated in the ACS and reach peak at 2h after onset of chest pain and start returning to baseline at 6h. IMA has been cleared by the US Food and Drug Administration as a biomarker to exclude myocardial ischaemia [5]. IMA is also a promising biomarker for the diagnosis of acute heart failure and assessment of the effect of inotropic therapy [6].

Efficacy of IMA

In a study, sensitivity of IMA at presentation for an ischaemic-origin chest pain was 82%, compared with 45% of ECG and 20% of cardiac troponin type T (cTnT). IMA used together with cTnT or ECG, had a sensitivity of 90% and 92%, respectively. All the three tests combined, identified 95% of patients whose chest pain was attributable to ischemic heart disease. A meta-analysis spanning more than 1800 patients concluded that combining negative electrocardiogram (ECCG) changes, negative troponin and negative IMA significantly increased the sensitivity and negative predictive value (NPV) to 94.4% and 97.1% for excluding ACS, and to 89.2% and 94.5% for longer term outcomes, respectively [5,7].

Limitations of IMA

IMA elevates in multiple ischemic conditions as stroke, pulmonary embolism or mesenteric artery occlusion. In a previous study, 97.7% of patients diagnosed to have pulmonary embolism (PE) had high IMA values, compared to the control group [8]. Another study on 118 patients presenting within 3 h of the onset of an acute neurological
deficit (84 brain infarctions) concluded that during the first 24 h, IMA levels significantly increased in brain infarction patients [9]. IMA is shown to be elevated in diabetic patients. Blood IMA level and IMA/albumin ratio significantly increase in adult patients who experienced seizures. Ischemia-modified albumin may be considered as a useful biomarker in the differential diagnosis of seizure [10]. A study reported that IMA was significantly elevated during pre-eclampsia up to delivery, compared with healthy pregnant women. Elevations of IMA have also been noted in anemia or in chronic kidney disease. Different causes of elevated IMA were given in (Table 1).

PRIMA study concluded that the diagnostic accuracy of IMA does not support its use for diagnosis of ACS in patients with acute chest pain. Their results showed lower sensitivity, lower NPV and narrow diagnostic time window of IMA [11]. Some researchers believe that IMA might not actually reflect myocardial ischaemia. Other hypotheses state that the release of IMA may depend on reperfusion-induced events rather than ischemia per se. To overcome this debate on IMA as a diagnostic marker for acute coronary ischaemia, we offer this work.

Materials and Methods

Study population

The present comparative cross-sectional observational study was conducted at the Departments of Cardiology and Medical Biochemistry in Benha University Hospitals from March 2014 to January 2015. This study was approved by the ethics committees of Benha University, Egypt. All the participants provided informed consents.

We enrolled 60 patients with age group of 30 to 70 years, who were admitted to the Cardiac Care Unit (CCU) with acute chest pain of less than 3 hours before admission plus normal ECG or non-specific ST-T changes at presentation. All patients were diagnosed by physicians who were blinded to the results of the IMA.

Exclusion criteria

- Chest pain duration for more than 3 hours before admission.
- Other clinical conditions of ischaemic distress such as pulmonary embolism, recent brain infarctions or mesenteric artery occlusion.
- Clinical conditions that associated with hypoalbuminemia and could affect IMA serum levels such as chronic liver diseases and acute or chronic renal failure.
- Patients who experienced recent attacks of seizures.
- Patients with previous ACS, PCI or CABG.
- Also patients with ischaemic/infarction evidence on the presenting ECG were excluded.

Methods

- History and physical examination: Stressing on chest pain criteria.
- Serial 12-lead electrocardiogram (ECG) at time of admission, 2hrs, 4hrs, 6hrs and 8hrs during admission to detect any ischaemic/infarction changes (ST segment elevation or depression).
- Trans thoracic Echocardiography for detection of wall motion abnormalities and left ventricular dysfunction.
- Resting wall motion abnormalities were recorded, that include hypokinesia or akinesia of one segment or more. Full RV assessment was done to rule out clinically suspected massive or sub massive pulmonary embolism. Echocardiographic examination was made by using general electric system vivid-3 machine with 2.5-3.5 MHZ probe.
- All echocardiography reports were interpreted by cardiologists who had more than 10 years of experience in echocardiography field.
- All patients underwent serial IMA and cTnT measures:
  - Detection of troponin-t at presentation and eight hours later by Enzyme Linked Fluorescent Assay (ELFA) using Biomerieux Mini VIDAS automated immunoassay system, Italy, according to manufacturer instructions of the kits. Cut off value was 0.04 ng/dl
  - Detection of ischemia modified albumin (IMA) at presentation and eight hours later by enzyme Linked Immunosorbent Assay (ELISA) [12] using human Ischemia Modified Albumin, IMA ELISA kit, Wuhan EIAab Science Co., Ltd, China. Cut off value was 75 ng/dl.

Serum sample collection: 5 ml blood was collected by venipuncture from the anticubital vein of the forearm of each subject under aseptic conditions and it was centrifuged for serum collection. The blood was allowed to clot by leaving it undisturbed at room temperature for 15-30 minutes. It was centrifuged at 1000-2000 xg for 10 minutes in a refrigerated centrifuge for clot removal and serum separation. Specimens were frozen at – 20°C.

Other modalities as CT angiography or D-Dimer test were used to exclude other possible etiologies which could mimic the results of IMA as pulmonary embolism, cerebrovascular ischemia or acute mesenteric ischemia.

Study design

Patients were divided into two groups: according to the discharge diagnosis

- Non-ischaemic chest pain group
- Ischaemic chest pain group

The classification was based on the following findings:-
Ischemic chest pain was diagnosed by any or combination of:

- Typical chest pain at presentation.
- New ischemic changes in serial ECG (Specific ST or T wave

Table 1: Non cardiac causes of raised ischaemia modified albumin that could mimic acute coronary syndrome.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolism with/without deep venous thrombosis</td>
<td></td>
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<tr>
<td>Thromboembolic occlusion of superior mesenteric artery</td>
<td></td>
</tr>
<tr>
<td>Acute neurological deficit (brain infarctions) , acute attacks of seizures</td>
<td></td>
</tr>
<tr>
<td>Diabetics with poor glycaemic control</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td></td>
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<tr>
<td>Any inflammation via oxidative stress</td>
<td></td>
</tr>
<tr>
<td>Pre-eclampsia up to delivery</td>
<td></td>
</tr>
<tr>
<td>Ovarian torsion</td>
<td></td>
</tr>
<tr>
<td>Chronic hypoxia or carbon monoxide (CO)-poisoned patients</td>
<td></td>
</tr>
</tbody>
</table>
changes)
- Positive cardiac biomarkers (Troponin T).
- Positive echocardiographic findings of (ischaemic wall motion abnormalities).

Non-ischemic chest pain was diagnosed when the above criteria were absent.

**Statistical analysis**

The collected data were tabulated and analyzed using SPSS version 16 software (SpssInc, Chicago, ILL Company). Categorical data were presented as number and percentages while quantitative data were expressed as mean ± standard deviation, median, range and IQR. Fisher’s exact test, Spearman’s correlation coefficient (rho), Man Whitney U test and Kruskal Wallis test were used as tests of significance. ROC curve was used to determine cutoff values of IMA & cTnT with optimum sensitivity and specificity in diagnosis of ischemic chest pain. The accepted level of significance in this work was stated at 0.05 (P<0.05 was considered significant) [13].

**Results**

Of the 60 enrolled patients there were 26 patients (43.3%) with a final diagnosis of non-ischaemic chest pain and 34 patients (56.7%) with a final diagnosis of ischemic chest pain (Figure 1). The baseline demographic and clinical characterizations of the study population were given in Table 2. The mean age and male sex ratio were significantly higher (p<0.001) in the patients with ischemic chest pain as compared to those with non-ischemic chest pain.

**Values of IMA and cTnT in ischemic chest pain and non-ischemic chest pain groups**

The IMA mean levels were significantly higher (p<0.001) in the patients with ischaemic chest pain as compared to those with non-ischaemic chest pain both at presentation and after 8 hours (297.76 ng/dl vs 76.15 ng/dl & 795.3 ng/dl vs. 247.92 ng/dl) respectively. The mean values of serum cTnT were significantly higher (P<0.001) in the patients with ischaemic chest pain as compared to those with non-ischaemic chest pain at presentation and after 8 hours (0.01 ng/dl versus 0.41 ng/dl & 0.01 ng/dl versus 2.48 ng/dl) respectively (Table 3).

**Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of cardiac markers**

Sensitivity of IMA was (70.6% and 91.2%) at presentation and 8 hours of admission while specificity was (65.4% and 76.2%) at presentation and 8 hours of admission.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of different tests (IMA and cTnT) used alone or in combination were described in Tables 4 and 5.

Combined use of IMA and cTnT significantly improved the sensitivity and the negative predictive value to (85.3% and 77.3%) respectively in comparison to both tests alone (p = 0.001), while this combination not improved the specificity or positive predictive value in comparison to both tests alone (Table 4).

After 8 hours, more improvement of the sensitivity, and the negative predictive value were obtained when IMA and cTnT were used in combination (100% for both) (p = 0.001). While this combination not improved the specificity or positive predictive value in comparison to both tests alone (Table 5).

**Discussion**

Diagnosis of ischaemia is difficult in patients presenting with acute chest pain, particularly those with un-interpretable baseline ECG [14]. Although cardiac ischaemia is highly probable in the presence of ST segment or T wave changes, regional wall motion abnormalities or myocardial perfusion defects, are frequently absent in patients presenting to the emergency department (ED) with acute chest pain. Confounding factors such as early repolarization, left ventricular hypertrophy, and left bundle branch block often preclude reliable ST segment analysis [15]. Cardiac troponins take about four to six hours to be detectable in the circulation and they do not necessarily rise in blood with reversible ischaemia [16]. There is a need for early and sensitive markers of cardiac ischemia. IMA is a new marker of ischemia that appears in the early few minutes of ischemia. IMA & cTnT with optimum sensitivity and specificity in diagnosis of ischemic chest pain. The accepted level of significance in this work was stated at 0.05 (P<0.05 was considered significant) [13].

The present study aimed to evaluate the role of IMA as an early marker for diagnosis or rule out acute coronary syndrome in patients presenting with acute chest pain versus and in combination to cardiac troponin T (cTnT). In the present study, ischemic chest pain as a discharge diagnosis was present in (56.7%) of our study population (Figure 1). Previous studies reported more or less similar results
Ischemia modified albumin (IMA) as a new biomarker for the early diagnosis of acute coronary syndrome.

# Table 3: Ischemia modified albumin (IMA) and Troponin T mean values among studied population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non Ischemic (N=20)</th>
<th>Ischemic (N=34)</th>
<th>Z of MWU test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMA at presentation</td>
<td>43.5-99.75 76.15 ± 46.33</td>
<td>55-425.2 297.76 ± 234.64</td>
<td>3.64</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IMA at 8 hours</td>
<td>145.75-385 247.92 ± 124.34</td>
<td>525.7-1004.5 795.26 ± 321.15</td>
<td>5.92</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>cTnT at presentation</td>
<td>0.01-0.01 0.01 ± 0.00</td>
<td>0.01-0.5 0.41 ± 1.51</td>
<td>3.83</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>cTnT at 8 hours</td>
<td>0.01-0.01 0.01 ± 0.00</td>
<td>0.42-2.87 2.48 ± 2.98</td>
<td>6.88</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

SD = Standard deviation.

# Table 4: Sensitivity, specificity, PPV and NPV of cardiac markers at presentation.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Cut off</th>
<th>Sensitivity%</th>
<th>Specificity%</th>
<th>PPV%</th>
<th>NPV%</th>
<th>Accuracy%</th>
<th>AUC</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMA</td>
<td>≥75ng/dl</td>
<td>70.6%</td>
<td>65.4%</td>
<td>72.7%</td>
<td>63%</td>
<td>77.5%</td>
<td>0.78</td>
<td>0.66-0.89</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>cTnT</td>
<td>≥0.04ng/dl</td>
<td>44.1%</td>
<td>100%</td>
<td>100%</td>
<td>42.2%</td>
<td>72.1%</td>
<td>0.72</td>
<td>0.59-0.85</td>
<td>0.004</td>
</tr>
<tr>
<td>IMA + cTnT</td>
<td>85.3%</td>
<td>65.4%</td>
<td>76.3%</td>
<td>77.3%</td>
<td>75.3%</td>
<td>75%</td>
<td>0.75</td>
<td>0.62-0.88</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Marker</th>
<th>Cut off</th>
<th>Sensitivity%</th>
<th>Specificity%</th>
<th>PPV%</th>
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<th>Accuracy%</th>
<th>AUC</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMA</td>
<td>≥75ng/dl</td>
<td>91.2%</td>
<td>76.2%</td>
<td>76.9%</td>
<td>89.3%</td>
<td>94.9%</td>
<td>0.95</td>
<td>0.89-1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>cTnT</td>
<td>≥0.04ng/dl</td>
<td>97.1%</td>
<td>96.2%</td>
<td>97.1%</td>
<td>96.2%</td>
<td>98.2%</td>
<td>0.98</td>
<td>0.95-1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IMA + cTnT</td>
<td>100%</td>
<td>96.2%</td>
<td>97.1%</td>
<td>100%</td>
<td>96.2%</td>
<td>98.5%</td>
<td>0.985</td>
<td>0.95-1.0</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

# Table 5: Sensitivity, specificity, PPV and NPV of cardiac markers after 8 hours.

[18,19]. These findings highlight the need for rapid, simple, non-invasive and accurate test for diagnosis or ruling out ischemia as the cause of acute chest pain. This has a major clinical advantage in directing the proper anti-ischaemic measure at the proper time and excluding those with non-ischemic chest pain to avoid unnecessary treatment.

The results of this study revealed that patients with ischaemic chest pain on discharge had significantly higher serum IMA levels when compared to patients with non-ischaemic chest pain both at presentation and after 8 hours (297.8 and 795.3 ng/dl versus 76.2 and 247.9 ng/dl respectively), p<0.001) (Table 3). This finding may be explained by the fact that cardiac ischaemia which is a state of oxidative stress could cause as much or more damage to serum albumin and the surrounding tissues as ischaemia itself. Different mechanisms have been postulated for the generation of IMA, early after cardiac ischaemia. Either ischaemia or a reperfusion may include sodium and calcium pump disruptions, and free iron and copper ion exposures. Most of these conditions occur in vivo, within minutes after the onset of acute myocardial ischaemia [20].

The sensitivity, specificity, positive and negative predictive values were estimated in the present study based on the using of 75 ng/dl as a cut off value for IMA and 0.04 ng/dl for cTnT. The discharge diagnosis of ischaemic versus non-ischaemic chest pain based on the following tests: clinical, ECG, Echocardiography & cTnT (Tables 4 and 5).

At presentation, the sensitivity of IMA was 70.6% while that of cTnT was 44.1%. When IMA was combined with cTnT the sensitivity has raised to 85.3% (Table 3). After 8 hours, the sensitivity of IMA was 91.2% while that of cTnT was 97.1% when IMA was combined with cTnT the sensitivity has risen to 100%. These findings were highly significant (Table 5).

In the present study, the sensitivity and NPV of IMA at presentation were greater as compared to that of cTnT (70.6% & 63% versus 44.1% & 42.2%). These findings support that IMA can be used as an independent parameter to cTnT to rule out ACS in early presentation.

The combination of the IMA and the cTnT results improved the sensitivity and NPV of the detection of coronary ischaemia up to 100% both at presentation and after 8 hours. Our results were in agreement to Sangita et al. 2013 which had revealed that a combination of the IMA and cTnT results had improved the sensitivity to 96% [21]. Previously Sinha et al. also evaluated IMA for the diagnosis of cardiac ischaemia in 208 patients. IMA had a higher sensitivity than the 12-lead ECG and initial cTnT levels for the diagnosis of ACS, whereas the combination of cTnT and IMA identified 95% of patients whose chest pain was attributable to ischaemic heart disease [6]. Peacock et al. in a meta-analysis concluded that when the IMA result is used alone it has a 91% negative predictive value for excluding ACS, which increases to 97% when it is used in combination with negative cTnT measurements and a normal or non-diagnostic ECG [22].

Lack of specificity and PPV of IMA in diagnosis of ACS alone and in combination with TnT in this study doesn’t underestimate its role as a negative marker for acute ischaemia and was explained by different non cardiac conditions in which IMA could be elevated as marked hyperglycemia, or subclinical inflammatory conditions (Table 1).

Cardiovascular diseases (CVD) are the major cause of death all over the world. The identification of markers that allow early detection of such diseases and/or their progression is essential in order to adopt the best actions to reduce the worsening of clinical condition. Our results indicate clearly that addition of IMA to the current standard tests for diagnosis of ACS will improve the ability to rule out patients without ACS & to identify ischaemic patients who are missed by current diagnostic strategies and thus could benefit from earlier treatment, and more confidently to shorten the stay in...
ED. IMA is a non-specific marker for diagnosis of ACS and should not be used to confirm the diagnosis. Physicians have tried to develop further detectable molecules in order to improve the detection of the early moments of CVD and prevent their development. Soluble ST2 (suppression of tumorigenicity 2) is a blood protein that acts as a receptor for interleukin-33. It seems to be markedly induced in mechanically overloaded cardiac myocytes. Many clinical studies try to identify the role of ST2 derived-protein as an early marker of cardiovascular diseases [23].

Study Limitations

The relatively limited number of the patients could limit the strength of results and conclusion obtained from this study.

Conclusion and Recommendations

This study lay in the fact that the measurements of serum IMA could aid in the diagnosis of ACS in patients with ischaemic pain, whose ECG changes were normal or non specific. IMA (<75 ng/dl) can be used as an independent parameter or in addition to cardiac troponins to rule out cardiac ischemia in such patients. This combination seems to have clear potentials of time saving and a shortened stay in the ED.

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References


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