Ischemia Modified Albumin, a Marker of Acute Ischemic Events: A Pilot Study

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Abstract. Ischemia modified albumin (IMA) is a relatively new marker for evaluating patients with cardiac ischemia. Data are emerging on its potential role in non-cardiac ischemic events. In this pilot study we evaluated the utility of IMA in diagnosing acute coronary syndromes (ACS), assessed its role in the diagnosis of non-cardiac ischemia, and correlated its efficacy with troponin T (TnT). Serum levels of IMA were measured in 89 sequential patients who presented to the emergency room with chest pain for which serum TnT was ordered. The patients were classified into 4 groups based on their IMA and TnT results and discharge diagnoses. The data were analyzed with Fischer’s exact test. Multivariate logistic regression analysis relating acute coronary syndrome (ACS) to the combination of TnT and IMA was also performed. The results showed that IMA was a useful marker for the diagnosis of ACS. There was a significant relationship between TnT and IMA (p = 0.032), suggesting that both these biomarkers added significant information about the presence of ACS (p = 0.028) and may be useful for triage of patients who present to the emergency room with chest pain. Serum IMA was also increased in a small proportion of patients with symptoms of stroke, suggesting that it should be considered a marker of acute ischemic events and not specific for cardiac ischemia.

Keywords: chest pain, troponin T, ischemia modified albumin, acute coronary syndrome, stroke

Introduction

Approximately 6 million people in the United States are admitted to hospitals each year with chest pain suggestive of acute coronary syndrome (ACS) [1]. Of these, only 17% are finally diagnosed with ACS [1]. Not infrequently, patients with suspected ACS have normal, non-diagnostic, or equivocal electrocardiograms (EKG) [2,3] and normal cardiac troponin levels at the time of admission. Currently, sensitive and specific biochemical markers are available for the identification of myocardial necrosis but not, unfortunately, for ischemia, which continues to pose a diagnostic challenge. A relatively new marker for evaluating patients with chest pain is ischemia modified albumin (IMA), which is produced during myocardial ischemia. Ischemia causes structural changes to the N-terminus of serum albumin that reduce its capacity to bind Co2+ and Ni2+. These changes are presumed to be related to the production of reactive oxygen species during ischemia and reperfusion, hypoxia, and acidosis [4].

During the past few years, several studies have evaluated the performance of IMA in cardiac patients. Serum IMA has been shown to be a rapidly rising sensitive marker for diagnosis of myocardial ischemia [5,6]. The albumin cobalt-binding test (ACB) is the first US FDA-cleared assay to detect IMA in myocardial ischemia. This test measures the amount of unbound cobalt
spectrophotometrically, which is an indirect measure of IMA levels in the serum. A recent study has shown that IMA is highly sensitive for the identification of ACS and that, in combination with an EKG, it has both high sensitivity and negative predictive value [7]. The goal of this pilot study was to confirm these findings and to evaluate the relationship of serum troponin T (TnT) and IMA levels in patients with ACS. Since the role of IMA in non-cardiac ischemia has not been clearly understood, we also studied patients with chest pain who were diagnosed with ischemic stroke.

Materials and Methods

Patients. In this retrospective study, we assessed 89 patients who came sequentially to the emergency room between December 2004 and January 2005. All these patients presented with chest pain and were subsequently admitted, either for observation in the emergency room or treatment in the hospital. The relevant clinical and diagnostic information on these patients was collected from their medical records. Cardiac markers were measured in the emergency room as a part of the chest pain protocol. Serum troponin T was measured from the first blood sample drawn in the emergency room (designated as 1st TnT), followed by subsequent measurements at regular intervals following admission, so as to detect peak levels (designated Max TnT). The serum samples were all frozen at -70°C within one hr of collection. IMA was measured only in the first sample drawn in the emergency room as a part of this study. The study was approved by the hospital’s Institutional Review Board (IRB).

Cardiac troponin T assay. Serum TnT levels were measured by an electrochemiluminescence assay with the Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, IN); the reference range was 0.00-0.03 ng/ml. A troponin T concentration >0.03 ng/ml was considered a positive result.

Albumin cobalt-binding test for IMA assay. Frozen serum samples were gently vortexed after thawing. Repeat freeze-thaw cycles were avoided. IMA was measured immediately after thawing, using the albumin cobalt-binding kit (Ischemia Technologies, Denver, CO) and the Cobas MIRA-Plus analyzer (Roche Diagnostics); the reference interval was 53-117 U/ml. An IMA level ≥117 U/ml was considered positive, as recommended by the kit manufacturer.

Classification based on IMA and TnT results. The patients were classified into 4 groups based on their serum IMA and TnT results: Group A: normal IMA and TnT; Group B: elevated IMA and normal TnT; Group C: elevated IMA and elevated TnT; and Group D: normal IMA and elevated TnT.

Discharge diagnoses. All the patients were admitted to the hospital from the emergency room and received institutional care. The patients were classified into the following 4 categories based on their diagnoses at the time of discharge:

1. Cardiac chest pain, ACS related: This group included patients with stable, unstable, or variant angina, and/or acute myocardial infarction. These patients had chest pain with one or more of the following symptoms: radiation, chest pressure/tightness, shortness of breath, lower jaw pain, left arm pain, epigastric pain, syncope, hypotension, and palpitations.

2. Cardiac chest pain, non-ACS related: This group included patients with hypertension, congestive cardiac failure, and/or arrhythmias. They presented with chest pain with one or more of the following findings: elevated blood pressure, lower extremity edema, and palpitations. Their EKG was either negative, equivocal with non-specific ST-T changes, or diagnostic for arrhythmias.

3. Stroke: Patients in this group presented with chest pain and one or more of the following symptoms: progressive neurological deficit, hemiplegia, sensory or motor impairment, cranial nerve palsies, and intra-cranial hemorrhage.

4. Non-ischemic chest pain: Patients in this group had chest pain with one or more of the following features: no classical symptoms of myocardial ischemia, non-diagnostic EKG, history of diabetes and/or hypertension, evidence of pleural, pericardial or pulmonary disease, and history or evidence of trauma.
Clinicopathologic correlation and statistical analysis. The final discharge diagnoses in all the patients were compared with their TnT and IMA results to determine the utility of IMA and to assess the relationship between these biomarkers. The data were analyzed by Fischer’s exact test. Multivariate logistic regression analysis was used to study the relationships of serum TnT and IMA levels for the diagnosis of ACS.

Results

Demographic and clinical characteristics of the study groups (Table 1). There was a significant difference in the age of the patients (p = 0.013) among the groups. Significant difference was also seen among the groups with respect to the history of smoking (p = 0.041). However, neither of these clinical parameters correlated significantly with the TnT or IMA values, due to the small size of the study sample. A majority of the patients in each of the four groups was male. Other clinical parameters such as hypertension, hyperlipidemia, and diabetes mellitus were not significantly different among the groups. The past medical history was significant for a previous myocardial infarction (MI) in 8 of the 19 patients (42.1%) in group B and 4 of the 6 patients (66.6%) in group D. All 19 patients in group B with elevated IMA had baseline TnT levels of ≤0.01 on presentation to the ER. Only one of these patients had a subsequent rise in TnT, with a Max TnT of 0.12 ng/ml. Patients in group C had higher TnT levels at the time of presentation (1st TnT) compared to those in group D. However this was not statistically significant (p = 0.077). The positive and negative TnT and IMA values from all the patients were plotted in a 2x2 table and compared using Fischer’s exact test. A significant relationship between the two biomarkers was found (p = 0.032).

Correlation of IMA and TnT values with discharge diagnoses (Table 2). Four of the 89 patients died following admission. Two deaths were in group A, one in group B and one in group D. These cases were included in the final analysis, since they all had the initial serum TnT and IMA levels measured.

A majority of the patients in group A (34/57) had non-cardiac chest pain. Their various discharge diagnoses included diabetic ketoacidosis, anxiety disorders, trauma, and chest pain not otherwise specified. Twenty-three of 57 patients (40%) had cardiac chest pain, either ACS (n = 8) or non-ACS (n = 15) related, with normal TnT and IMA. Of the 8 patients with cardiac chest pain, ACS related, 5 had stable angina and 3 had variant angina at the time of admission.

In group B, 11 of 19 patients (58%) had cardiac chest pain, either ACS (n = 7) or non-ACS (n = 4) related, with normal TnT and elevated IMA. Five of the 7 patients with ACS-related cardiac chest

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>57 (64.0%) Normal TnT Normal IMA</td>
<td>19 (21.3%) Elevated IMA Normal TnT</td>
<td>7 (7.8%) Elevated IMA Elevated IMA</td>
<td>6 (6.7%) Elevated TnT Normal IMA</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.7 (14) Normal TnT</td>
<td>53.3 (15.8) Elevated IMA</td>
<td>58.1 (16.1) Elevated IMA</td>
<td>65.6 (8.2) Elevated IMA</td>
<td>0.013</td>
</tr>
<tr>
<td>Men</td>
<td>30 (51.7%) Normal TnT</td>
<td>13 (68.4%) Elevated IMA</td>
<td>7 (71.4%) Elevated IMA</td>
<td>4 (66.6%) Elevated IMA</td>
<td>0.415</td>
</tr>
<tr>
<td>Smoking</td>
<td>43 (74.1%) Normal TnT</td>
<td>12 (63.1%) Elevated IMA</td>
<td>5 (71.4%) Elevated IMA</td>
<td>1 (16.6%) Elevated IMA</td>
<td>0.041</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37 (63.7%) Normal TnT</td>
<td>15 (78.9%) Elevated IMA</td>
<td>6 (85.7%) Elevated IMA</td>
<td>100% Elevated IMA</td>
<td>0.183</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>10 (17%) Normal TnT</td>
<td>7 (36.8%) Elevated IMA</td>
<td>2 (28.5%) Elevated IMA</td>
<td>2 (28.5%) Elevated IMA</td>
<td>0.331</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (18.9%) Normal TnT</td>
<td>5 (26.3%) Elevated IMA</td>
<td>3 (42.8%) Elevated IMA</td>
<td>2 (33.3%) Elevated IMA</td>
<td>0.490</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>11 (18.9%) Normal TnT</td>
<td>8 (42.1%) Elevated IMA</td>
<td>1 (14.2%) Elevated IMA</td>
<td>4 (66.6%) Elevated IMA</td>
<td>0.067</td>
</tr>
<tr>
<td>Angina at presentation</td>
<td>8 (13.7%) Normal TnT</td>
<td>5 (26.3 %) Elevated IMA</td>
<td>3 (42.8%) Elevated IMA</td>
<td>2 (33.3%) Elevated IMA</td>
<td>0.227</td>
</tr>
<tr>
<td>1st TnT (ng/ml)</td>
<td>0.01 (0.00) Normal TnT</td>
<td>0.01 (0.004) Elevated IMA</td>
<td>0.38 (0.39) Elevated IMA</td>
<td>0.07 (0.03) Elevated IMA</td>
<td>0.077</td>
</tr>
<tr>
<td>Max TnT (ng/ml)</td>
<td>0.02 (0.00) Normal TnT</td>
<td>0.02 (0.025) Elevated IMA</td>
<td>0.41 (0.39) Elevated IMA</td>
<td>1.91 (0.41) Elevated IMA</td>
<td>0.362</td>
</tr>
<tr>
<td>IMA (U/ml)</td>
<td>98.6 (11.4) Normal TnT</td>
<td>129.0 (10.1) Elevated IMA</td>
<td>136.0 (18) Elevated IMA</td>
<td>102.0 (9.1) Elevated IMA</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TnT = serum troponin T; IMA = serum ischemia modified albumin; Max TnT = maximum serum troponin T level.
pain had angina confirmed by EKG at the time of admission (3 stable and 2 unstable angina). Their initial TnT level was within the normal range, but the IMA level was elevated. All of them received treatment based on the EKG results, without elevation of subsequent TnT values. Five of the 6 patients with a discharge diagnosis of stroke had hypertension. All 6 had symptoms of a transient ischemic attack at the time of admission to the ER and subsequently developed ischemic stroke. Their EKG’s and cardiac markers were negative and the IMA levels were 130, 118, 123, 124, 126, and 135 U/ml. This relationship was statistically significant (p = 0.003).

In group C, all of the 7 patients (100%) had cardiac chest pain, either ACS (n = 5) or non-ACS (n = 2) related, with elevated TnT and IMA. Three of the 5 patients with ACS-related cardiac chest pain, had unstable angina at the time of admission. The remaining 2 patients had evidence of MI at the time of presentation.

In group D, 5 of 6 patients had cardiac chest pain, either ACS (n = 3) or non-ACS (n = 2) related, with elevated TnT and normal IMA. Two of the 3 patients with ACS-related cardiac chest pain developed MI following admission. Their serum TnT levels were elevated at the time of admission but their serum IMA levels were 114 and 104 U/ml, respectively.

A multivariate logistic regression model was used to relate acute coronary syndrome as a dependent variable to the combination of TnT and IMA. The logistic model demonstrated that after controlling for the diagnostic effect of TnT (p = 0.003), the presence of an elevated IMA added significant information (p = 0.028). This indicates that both TnT and IMA independently predict the risk of presence of cardiac chest pain.

### Discussion

The symptoms of patients with myocardial ischemia and/or infarction can be diverse. Although not specific for myocardial ischemia/infarction, chest pain (CP) is one of the earliest and most common symptoms in patients presenting to the ER. We therefore used CP as a surrogate clinical marker for cardiac ischemia/infarction in the present study. There was a significant relationship between TnT and IMA, suggesting that the 2 biomarkers are closely related to each other in detecting myocardial damage in patients presenting with chest pain. Unlike TnT, a marker of myocardial necrosis, IMA appears to reflect cardiac ischemia or ischemia-reperfusion injury, expressed as reduced metal binding capacity of albumin. This is in agreement with previous studies [5,6,9].

An ability to detect ischemia before myocyte destruction would allow earlier and more accurate management decisions for patients suspected of having cardiac ischemia than is currently possible based on serum troponin, CK-MB, or myoglobin.
levels. Previous studies have demonstrated that elevation of IMA levels precedes cardiac troponin elevations in patients with cardiac ischemia [7,8]. This early prediction by a biochemical marker of ischemia is important as it may improve the ability to stratify acute chest pain patients and guide therapeutic decisions.

Although IMA is a sensitive marker for ischemia, as seen in our study, its sensitivity decreases especially in conditions associated with transient/reversible ischemia. This may explain the IMA levels within the reference range in group A patients with variant and stable angina. Another factor responsible for these false negative IMA values is the presence of lactic acid in these patients secondary to prolonged ischemia and acidosis. Elevated lactic acid levels have been shown to be associated with a decrease in IMA levels, the cause of which is not known [10]. Although corroborative studies evaluating this interference are lacking, we speculate that increased lactate displaces the copper bound to albumin. This, in turn, results in an increased number of binding sites on the albumin molecule for cobalt, thereby decreasing the level of IMA. The third possible cause for a false negative IMA, especially in patients of group D, may be delayed presentation to the ER. It is known that IMA levels rise within minutes after ischemia and return to baseline within 4 to 6 hr [5].

Of the 18 patients in groups B and C with cardiac chest pain that was ACS and non-ACS related, 11 had elevated IMA in the presence of normal troponin T. Seven of these patients had a history of cardiac ischemia based on EKG and/or cardiac marker studies. In 4 patients with non-ACS related CP, although EKG and/or cardiac markers (including TnT) were negative, presence of an elevated IMA could indicate early ischemia. These results support the evidence that IMA is an early marker of ischemia, increases before any detectable change in cardiac troponins, and is elevated even in the absence of myocardial necrosis. This is especially useful to rule out ischemia in the emergency setting, thereby making IMA a potentially useful biomarker. A recent meta-analysis evaluating the role of IMA to rule out ACS in the emergency department showed a high negative predictive value of IMA, thereby helping to rule out ACS [11]. Although IMA is a useful marker for early detection of cardiac ischemia, serial measurements of IMA do not contribute significantly to predicting the outcomes in patients with chest pain who have not yet experienced a serious cardiac event [12].

A few studies have assessed the role of IMA in non-cardiac ischemic states. In the present study, 8 patients in group B had an elevated IMA in the absence of cardiac ischemia. Six of these 8 patients presented with features of transient ischemic attack and progressed to develop ischemic stroke. They had chest pain with negative EKG and TnT. However, their IMA levels were elevated at the time of presentation. Chi-square analysis revealed a significant association of elevated IMA levels with a diagnosis of ischemic stroke (p = 0.0029). Our results are in agreement with a preliminary study by Abboud et al [13] that showed that IMA is a biomarker for early identification of acute ischemic stroke [13]. Roy et al [14] reported that IMA concentrations are significantly lower immediately after exercise-induced leg ischemia in patients with peripheral vascular disease [14]. Two previous studies have assessed the effect of skeletal muscle ischemia on serum IMA levels in apparently healthy individuals [8,15]. A transient decrease in IMA concentrations has been observed immediately after exercise and/or skeletal muscle ischemia, followed by a delayed increase after 24 to 48 hr. It has been hypothesized that the immediate decrease may be attributable to interference in the IMA measurement by lactate produced during skeletal muscle ischemia [14]. We speculate that serum IMA levels may be elevated in non-cardiac ischemic states. Since susceptibility of cells to ischemia may vary from one organ to another, it would be critical to determine the optimal IMA level for the diagnosis of ischemia in various organs, especially the heart and brain. Further studies are required to evaluate the role of IMA in non-cardiac ischemia and to establish the optimum IMA cut-off levels in various ischemic states.

In conclusion, we found that serum IMA is a useful marker for the diagnosis of ACS. There is a significant relationship between the results of TnT, a measure of myocardial necrosis and IMA, a measure of ischemia, in evaluating patients with ACS. The high sensitivity of TnT coupled with the
high negative predictive value of IMA make them independent predictors of the risk of developing ACS. IMA may therefore be used in conjunction with TnT and EKG to triage patients who present to the ER with symptoms of ACS. Lastly, IMA is not specific for cardiac ischemia, which expands its potential role as a biomarker for acute ischemic events.

References


