Ischemia-Modified Albumin Improves the Usefulness of Standard Cardiac Biomarkers for the Diagnosis of Myocardial Ischemia in the Emergency Department Setting

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Key Words: Acute coronary syndrome; Biomarkers; Ischemia-modified albumin

Abstract

We studied the role of ischemia-modified albumin (IMA) with standard biomarkers (myoglobin, creatine kinase-MB [CK-MB], troponin I [TnI]) in assessment of 200 patients with suspected myocardial ischemia admitted to the emergency department. Every case was reviewed by a cardiologist. A clinical diagnosis of ischemia was assigned and correlated with biomarker test results. Of the patients, 25 (13.0%) had myocardial ischemia. Receiver operating characteristic curves demonstrated IMA as highly sensitive but somewhat poorly specific for the presence of ischemia (area under curve, 0.63; \( P = .01 \)). With a cut point of 90 U/mL, the Albumin Cobalt Binding Test had 80% sensitivity and 31% specificity for diagnosing ischemia and a negative predictive value of 92%. IMA was positive in 4 of 5 patients with electrocardiographic (ECG) evidence of ischemia and 16 of 20 patients with coronary ischemia but negative ECG. Among the same patients, the myoglobin–CK-MB–TnI triad had a sensitivity of 57%. The combination of IMA–myoglobin–CK-MB–TnI increased the sensitivity for detecting ischemia to 97%, with a negative predictive value of 92%. IMA is highly sensitive and has a high negative predictive value, which might improve the usefulness of standard biomarkers of myocardial ischemia.

Establishing a diagnosis of acute coronary syndrome in the clinical setting remains a challenging task. The advent of testing for cardiac biomarkers, such as myoglobin, creatine kinase (CK-MB), and the troponins has facilitated this process. Unfortunately, although these blood markers are extremely sensitive for the identification of patients with myocardial necrosis, their ability to identify patients with acute coronary ischemia remains limited because the spectrum of acute coronary syndromes also includes stable and unstable angina, both of which describe transient ischemic events without associated myocardial necrosis. In addition, myocardial necrosis is time-dependent, such that these highly sensitive and specific markers might give negative results on admission but give positive results hours later. As such, the usefulness of the standard biomarkers of myocardial necrosis for the confident exclusion of the diagnosis of myocardial ischemia at the time of admission remains limited. Thus, markers able to identify patients with myocardial ischemia without infarction might serve an important role in the clinical setting.

A candidate marker for the detection of myocardial ischemia is ischemia-modified albumin (IMA). During myocardial ischemia, several changes occur in the amino-terminus of albumin, which result in a significant change in the ability of albumin to bind transition metals, notably, cobalt.1 Therefore, if reliable, an assay measuring IMA might represent a promising marker for the identification of patients with myocardial ischemia, which, together with standard markers of myocyte necrosis, might be a superior screening method for patient evaluation to rule out acute myocardial ischemia. Accordingly, we studied the role of IMA together with myoglobin, CK-MB, and troponin I (TnI) for this use among...
patients admitted to an emergency department (ED) with symptoms suggestive of acute myocardial ischemia.

**Materials and Methods**

All protocols involved in this study were approved by an institutional review board.

**Patient Selection**

Data were collected for 200 consecutive patients admitted to an urban ED with manifestations suggestive of acute myocardial ischemia, including those such as chest pain with or without radiation, chest pressure, shortness of breath, lower jaw pain, left arm pain, epigastric pain, syncope, hypotension, new or increasing lower extremity edema, palpitations, and other symptoms suggestive of an anginal equivalent. Cardiac biomarkers of necrosis (myoglobin, CK-MB, and TnI) were measured in the ED as part of the standard of care at the Massachusetts General Hospital, Boston.

**Clinical Characteristics**

Demographics, clinical information, and hospital course following enrollment were recorded for each patient via review of the medical records, performed by individuals blinded to all biomarker results. Data analyzed included records of the ED evaluation, all relevant electrocardiograms (ECGs), echocardiography, stress-testing data, cardiac catheterization data, admission history and physical examination findings, hospital course documentation, and discharge summaries.

Electrocardiographic criteria used to support a clinical diagnosis of myocardial ischemia were new findings of ST segment elevation of 1 mm or more in 2 contiguous leads, ST segment depression of 1 mm or more in 2 contiguous leads, new left bundle branch block, and T-wave inversions of 3 mm or without radiation, chest pressure, shortness of breath, lower jaw pain, left arm pain, epigastric pain, syncope, hypotension, new or increasing lower extremity edema, palpitations, and other symptoms suggestive of an anginal equivalent. Cardiac biomarkers of necrosis (myoglobin, CK-MB, and TnI) were measured in the ED as part of the standard of care at the Massachusetts General Hospital, Boston.

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Following initial evaluation, patients were divided into categories based on the presence or absence of myocardial ischemia, and their demographics, clinical characteristics, hospital course, and biomarker results were compared.

**Serum Samples for Diagnostic Laboratory Examination**

Serum samples and heparinized whole blood samples were obtained at the time of admission in standard collection tubes without anticoagulants. Initially, the whole blood samples were used to measure myoglobin, CK-MB, and TnI on a near-patient point-of-care testing platform (Triage, Biorite, La Jolla, CA). The lowest detectable limits for these tests are as follows: myoglobin, 2.7 ng/mL; CK-MB, 0.75 ng/mL; and TnI, 0.19 ng/mL. Measurement for IMA was performed with the Albumin Cobalt Binding Test (Ischemia Technologies, Denver, CO) on a Roche Hitachi 911 platform (Roche Diagnostics, Indianapolis, IN). The lowest detectable limit for this test is reported by the manufacturer to be 10 to 18 U/mL.

**Statistical Analysis**

Data analysis was performed using SPSS statistical analysis software (SPSS, Chicago, IL). Univariate analyses between groups were done using $\chi^2$ cross-tabulations for categorical data and the Student $t$ test for continuous data. All $P$ values are 2-sided, with values less than .05 considered significant.

Following the identification of patients with and without myocardial ischemia, calculation of the sensitivity, specificity, and positive and negative predictive values for IMA and for parallel testing with the aggregate triple screen of myocardial necrosis biomarkers (myoglobin, CK-MB, and TnI) was performed.

**Results**

**Clinical Characteristics**

Of the 200 patients whose data were analyzed in a consecutive manner, 7 patients were excluded from the study because complete data about their clinical course could not be obtained. This left 193 patients for analysis. The majority of this population (172 [89.1%]) was admitted to the hospital following admission to the ED. Of the total population analyzed, 25 (13.0%) were judged as having myocardial ischemia at the time of admission, with 9 patients (4.7%) having acute MI and 16 patients (8.3%) with unstable angina pectoris.

Clinical characteristics of patients based on the presence or absence of myocardial ischemia differed significantly: patients with a diagnosis of ischemia were more likely to be older (mean ± SD age, 70.5 ± 16.9 years vs 65.4 ± 16.9 years; $P < .001$), to have had a previous diagnosis of coronary artery disease (17/25 [68%] vs 44/168 [26.1%]; $P < .001$), or to have undergone coronary revascularization (7/25 [28%] vs 17/168...
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[10.1%; P = .002]. Furthermore, patients with ischemia were more likely to have had previous congestive heart failure (5/25 [20%] vs 10/168 [6.0%; P = .002]. The presence of changes on the ECG suggestive of ischemia was more than twice as common among patients with a final diagnosis of an acute coronary syndrome (4/25 [16%] vs 12/168 [7.1%; P = .05).

Cardiac Biomarker Results

Assay for IMA, Cut Points, and Myocardial Ischemia

At the time of admission to the ED, the results from the Albumin Cobalt Binding Test for the detection of IMA were correlated with the adjudicated diagnosis of myocardial ischemia based on clinical data. Receiver operating characteristic curves demonstrated the assay for IMA to be highly sensitive but somewhat poorly specific for the detection of coronary ischemia (area under the ROC curve, 0.63; P = .01) [Figure II].

With the receiver operating characteristic curve as a guide, exploratory analysis of different cut points was performed [Table II]. With a diagnostic threshold (cut point) of 80 U/mL for the diagnosis of ischemia, the IMA assay was 100% sensitive but demonstrated a low specificity, 20%. The negative predictive value for the assay at this cut point was 100% for excluding the diagnosis of coronary ischemia. In an attempt to optimize sensitivity and specificity, we examined different diagnostic thresholds. At a cut point of 85 U/mL, the assay was highly sensitive; however, the specificity remained low. Again, with this cut point for the diagnosis of ischemia, the negative predictive value for ischemia remained high. At a cut point of 90 U/mL, this assay had a specificity of 80% and specificity of 31%. Using 90 U/mL as a diagnostic threshold for ischemia did not affect the negative predictive value, which remained high. Last, a cut point of 100 U/mL had a sensitivity of 64%, a specificity of 66%, and a negative predictive value of 82%.

ECG and IMA Results

Among the 25 patients with ischemia, only 5 (25%) had evidence on the ECG for ischemia (ST segment depression or elevation or a new left bundle branch block). Among these patients, the IMA result was negative in 1 patient (using a cut point of 90 U/mL). Among the 20 patients with ischemia but negative findings on the ECG, an IMA result of more than 90 U/mL correctly identified 16 of 20.

Markers of Myonecrosis, With or Without IMA

At the time of admission to the ED, the combination of myoglobin, CK-MB, and TnI had a sensitivity of 57% for the diagnosis of myocardial ischemia in the same population [Figure II], with the majority of patients having elevated levels of 2 or 3 markers.

By comparing myoglobin results with those for CK-MB, we found that myoglobin was elevated in 16 (64%) of patients with an acute coronary syndrome, while 11 (44%) had positive CK-MB results on admission to the ED. Furthermore, considering patients with 2 markers positive, myoglobin was elevated in 4 (16%) of patients, while CK-MB was elevated in 4 (16%). Last, among patients in whom only 1 marker was elevated on admission to the ED, myoglobin alone was elevated in 5 (20%) of patients subsequently given a diagnosis of acute coronary syndrome, in comparison with isolated CK-MB elevation, which was found in none of the patients with an ultimate diagnosis of acute coronary syndrome (P = .001).

When results of the IMA assay (using a diagnostic threshold for ischemia of 90 U/mL) were added to the panel of myoglobin, CK-MB, and TnI, the sensitivity for the diagnosis of myocardial ischemia of this combination was increased to
97%, with a negative predictive value of 92%. Patterns of biomarker results, incorporating IMA data, are detailed in Table 2. It is interesting that among patients with ischemia in whom IMA was accompanied by only 1 other marker of myonecrosis, myoglobin was elevated universally, suggesting these patients were early in the course following the onset of acute myocardial ischemia.

**Discussion**

The use of biomarkers for the identification of suspected acute coronary syndromes depends on the presence of myonecrosis as a surrogate indicator for myocardial ischemia. However, many patients have myocardial ischemia in the absence of myonecrosis, and markers such as myoglobin, CK-MB, and the troponins, although mainstays for the diagnosis of acute cardiac myonecrosis, thus are limited for the confident exclusion of coronary ischemia. Furthermore, the release of these markers is time-dependent; an initially negative result does not exclude the presence of MI. Therefore, a rapidly detectable, highly sensitive marker for myocardial ischemia would be desirable to identify patients with only ischemia and those early in the course of an acute coronary syndrome without evidence of myocardial necrosis. For such a marker to be useful, it should be accompanied by a high negative predictive value.

It has been reported that in the setting of myocardial ischemia, there are modifications to the amino acids of the N-terminus of the human albumin molecule. These modifications alter the N-terminus in such a way that it can no longer bind transition metals, such as cobalt. From this observation, an assay measuring the ability of albumin to bind cobalt was developed, which has been suggested to be useful for the detection of myocardial ischemia. In experimental models and in clinical studies, IMA has been shown to rise within minutes after the onset of ischemia, stay elevated for 6 to 12 hours, and return to normal within 24 hours. Furthermore, IMA has been shown to predict with high sensitivity subsequent elevation in the troponins in the clinical setting. An automated chemistry assay for the measurement of IMA is approved by the US Food and Drug Administration, is widely available, and has rapid turnaround times. Accordingly, we performed the present study to explore the feasibility and value of the Albumin Cobalt Binding Test for IMA when used together with standard markers of myocardial necrosis for the evaluation of patients with suspected acute coronary syndromes.

By using a diagnostic cut point of 90 U/mL, we found the assay for the measurement of IMA was sensitive for the diagnosis of myocardial ischemia at the time of clinical diagnosis and had a high negative predictive value. The results of IMA testing were additive to those of ECG and useful when used in conjunction with markers of myocardial necrosis. Consistent with the findings of previous studies, we found that standard biomarkers of cardiac myonecrosis had low sensitivity and negative predictive value for the confident diagnosis or exclusion of coronary ischemia at the time of initial evaluation in the ED. It is interesting that we found myoglobin of value for the early detection of patients with coronary ischemia when other markers of myonecrosis were negative. In this setting, IMA was elevated universally, offering complementary information to the myoglobin result.

Furthermore, we found that the combination of the triple screen plus IMA resulted in superior sensitivity for the detection of an acute coronary syndrome, with a simultaneous increase in the negative predictive value to 92%, largely by detecting patients with coronary ischemia and negative myoglobin or TnI results. As such, measurement of IMA together with myoglobin and TnI not only seems to augment sensitivity and, thus, potentially miss fewer patients with coronary ischemia but also might be a particularly useful strategy to confidently rule out myocardial ischemia. A similar biomarker strategy now is used to exclude the diagnosis of pulmonary
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Embolism with measurement of D dimer, which has been reported to have sensitivity and negative predictive values similar to those of IMA.\(^8,9\)

An appropriate setting in which to consider the use of the multimarker combination of IMA plus markers of myonecrosis would be for the rapid evaluation of low- to intermediate-risk patients with chest discomfort. Chest pain centers have been reported to allow for the complete and cost-effective evaluation of patients with low to intermediate pretest probability of having an acute coronary syndrome.\(^10,11\) The goal in such centers would be to rapidly and confidently diagnose or exclude MI, unstable angina, or exercise-induced ischemia among patients without prevalent high-risk features, such as changes on the ECG. The role of myoglobin in chest pain centers has been limited by its lack of specificity; however, together with myoglobin, the use of IMA might be useful for patients admitted to the ED early (ie, within 1 hour of symptom onset), permitting ruling out of myocardial ischemia in an earlier manner.

We propose a strategy incorporating rapid biomarker analysis \(\text{Figure 3}\) using the combination of highly sensitive markers rising soon after coronary ischemia begins (such as IMA plus myoglobin), together with a marker with a high degree of specificity,\(^11\) such as a troponin. Our data suggest that measurement of IMA plus myoglobin, followed by TnI testing, is an ideal marker strategy, offering high sensitivity, specificity, and negative predictive value. A negative value

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**Table 2**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Myoglobin (ng/mL)</th>
<th>CK-MB (ng/mL)</th>
<th>Troponin I (ng/mL)</th>
<th>IMA (U/mL)</th>
<th>No. of Positive Markers, Excluding IMA</th>
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<tr>
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<td>&gt;500.0</td>
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<td>1.4</td>
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<td>1.4</td>
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<td>&lt;0.2</td>
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CK-MB, creatine kinase, MB fraction; IMA, ischemia-modified albumin.

* Positive marker results are expressed in boldface type.

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**Figure 3**

Suggested flow diagram incorporating ischemia-modified albumin (IMA) testing into the diagnostic algorithm for patients admitted to the emergency department (ED) with chest pain. For patients with intermediate- or high-risk conditions, inpatient observation with serial troponin (Tn) testing (reserving coronary care unit [CCU]-level care for the highest risk patients) would be indicated. For those with low-risk conditions, a “rapid rule out” protocol combining IMA, myoglobin (Myo), and troponin testing provides high sensitivity and specificity with a strong negative predictive value. ECG, electrocardiogram.
would be helpful in excluding a diagnosis of myocardial ischemia early in the evaluation algorithm, while adding further clinician confidence in the myoglobin result if positive. Furthermore, a subsequent (correctly timed) troponin measurement would effectively confirm or exclude myonecrosis.

The limitations of this study include its small size and the heterogeneous nature of the patient population being examined. Furthermore, the prevalence of true ischemia in this patient subgroup was low, which affects the specificity of the markers studied. However, the goal was to study the use of IMA in a population of ED with concerning clinical manifestations.

We demonstrated that the addition of testing for a putative marker of myocardial ischemia, namely IMA, to standard markers of myocardial injury (in particular, myoglobin and TnI) is useful in a strategy for the evaluation of patients in the ED with suspected acute coronary ischemia. This is accomplished by allowing for improvement in the sensitivity of standard markers of myonecrosis, while retaining a strong negative predictive value. Larger studies of this promising marker are needed to further clarify its role in a definitive biochemical rule-out strategy.

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References


