Change in Ischemia-Modified Albumin and Its Clinical Significance During Exercise Stress Testing

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Background: There is little data about the additive effects of ischemia-modified albumin (IMA) on the exercise stress test (EST) used for the screening of ischemic heart disease. The relationship between myocardial ischemic burden and the change in IMA (ΔIMA) during EST was investigated.

Methods and Results: EST was performed using the Bruce protocol to evaluate chest pain or exertional dyspnea in 155 patients (men 89, 53±13 years). Blood samples for IMA were obtained before and immediately after EST. According to the EST results and the pattern of ΔIMA, patients were categorized into 3 groups (none was classified as EST(−)/ΔIMA(−)): (1) EST(−); (2) EST(+)/ΔIMA(−); and (3) EST(+)/ΔIMA(+). After EST, 60 of 155 (38.7%) patients were EST(+) and 14/60 (23.3%) were EST(+)/ΔIMA(+). Duke treadmill score was significantly lower in the EST(+)/ΔIMA(+) group compared with the other groups (-9.0±7.9, -1.7±4.2, 6.7±4.4, respectively, P<0.001); 43/60 (72%) patients with EST(+) underwent coronary angiography and the proportion of patients with a large ischemic burden was higher in the EST(+)/ΔIMA(+) group compared with the EST(+)/ΔIMA(−) group (72.7% vs 15.6%, P=0.001).

Conclusions: Increased IMA after EST suggests a large ischemic burden in coronary artery disease, so the ΔIMA during EST may be useful for predicting the severity of myocardial ischemia. (Circ J 2010; 74: 484–489)

Key Words: Exercise stress test; Ischemia modified albumin; Myocardial ischemia

The most recent data from the Centers for Disease Control show that in 2004, 5.6 million patients presented to US emergency departments (ED) with chest pain as their primary complaint. Because chest pain is 1 of many presentations of acute coronary syndrome (ACS), 15% of all ED visits (16.5 million patients per year) involve ECG testing and cardiac marker measurements as part of the evaluation and only 23% of patients are diagnosed as having coronary artery disease (CAD), including ACS. In the case of outpatient clinics, although treadmill exercise stress testing (EST) is widely available for the screening of CAD, false-negative and false-positive results are important clinical problems in the diagnosis of CAD. Therefore, a novel ischemic marker is needed for the detection with high diagnostic accuracy of early myocardial ischemia in patients with chest pain.

Ischemia-modified albumin (IMA) is considered a marker of myocardial ischemia, in contrast to the cardiac enzymes (creatine kinase-myocardial band and troponins) that are released when cardiac necrosis occurs. Ischemia, through hypoxia, acidosis and free radical injury, might induce changes in the capacity of the amino terminus of albumin to bind metals such as cobalt, copper, and nickel. On the basis of these biochemical changes, the albumin-cobalt binding test (ACB test: Ischemia Technologies Inc, Denver, CO, USA), which detects reduced albumin binding to cobalt, was developed to evaluate IMA in serum. IMA has been reported to increase after percutaneous coronary intervention (PCI) and in ACS, but there is little evidence of the additive effects of IMA on the results of EST for the screening of ischemic heart disease. In this study, we investigated the relationship between myocardial ischemic burden and the change in IMA (ΔIMA) during EST.

Study Population
The study population comprised 155 patients undergoing a treadmill EST for the evaluation of exertional dyspnea or chest discomfort at Uijungbu St Mary’s Hospital between January 2007 and December 2007. Criteria for exclusion included: (1) hemodynamically unstable patients with acute myocardial infarct or unstable angina; (2) patients who could not perform the EST because of underlying conditions (joint...
Usefulness of Ischemia-Modified Albumin

Table 1. Baseline Characteristics of the 3 Groups According to the Results of Exercise Stress Testing and the Change in Ischemia-Modified Albumin

<table>
<thead>
<tr>
<th></th>
<th>EST(−)(n=95)</th>
<th>EST(+)∆IMA(−)(n=46)</th>
<th>EST(+)∆IMA(+)(n=14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>52±14</td>
<td>55±11</td>
<td>56±16</td>
<td>0.29</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>50 (52.6)</td>
<td>29 (63.0)</td>
<td>10 (71.4)</td>
<td>0.27</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>28 (31.1)</td>
<td>20 (44.4)</td>
<td>6 (42.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>9 (10.0)</td>
<td>12 (26.7)</td>
<td>3 (21.4)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>20 (25.3)</td>
<td>13 (33.3)</td>
<td>4 (28.6)</td>
<td>0.66</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>129±15</td>
<td>133±16</td>
<td>134±14</td>
<td>0.33</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>69±12</td>
<td>70±13</td>
<td>68±16</td>
<td>0.66</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>89±21</td>
<td>87±17</td>
<td>90±20</td>
<td>0.87</td>
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<tr>
<td>Total cholesterol, mg/dl</td>
<td>185±37</td>
<td>181±52</td>
<td>183±54</td>
<td>0.92</td>
</tr>
<tr>
<td>Triglyceride, mg/dl</td>
<td>135±87</td>
<td>130±60</td>
<td>125±93</td>
<td>0.90</td>
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<tr>
<td>HDL-C, mg/dl</td>
<td>47±9</td>
<td>43±9</td>
<td>46±11</td>
<td>0.14</td>
</tr>
<tr>
<td>LDL-C, mg/dl</td>
<td>111±32</td>
<td>109±48</td>
<td>115±56</td>
<td>0.91</td>
</tr>
<tr>
<td>IMA (pre-EST), U/ml</td>
<td>82±16</td>
<td>86±15</td>
<td>84±12</td>
<td>0.28</td>
</tr>
<tr>
<td>IMA (post-EST), U/ml</td>
<td>71±13</td>
<td>75±16</td>
<td>93±17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>∆IMA, U/ml</td>
<td>−11±10</td>
<td>−11±8</td>
<td>9±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duke treadmill score</td>
<td>6.7±4.4</td>
<td>−1.7±4.2</td>
<td>−9.0±7.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Medical history

- Aspirin (%) 30 (31.6) 15 (32.6) 5 (33.3) 0.67
- ACEI or ARB (%) 7 (7.4) 5 (10.9) 3 (21.4) 0.24
- β-blockers (%) 13 (13.7) 8 (17.4) 3 (21.4) 0.49
- CCBs (%) 28 (29.5) 14 (30.4) 3 (21.4) 0.87
- Diuretics (%) 21 (22.1) 10 (21.7) 2 (14.3) 0.15
- Statins (%) 32 (33.7) 17 (37.0) 5 (35.7) 0.93

EST, exercise stress test; ∆IMA, change in ischemia-modified albumin; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CCBs, calcium-channel blockers.

Methods

Clinical data were obtained from a comprehensive review of each patient’s medical record using established criteria for hypertension, diabetes mellitus and hyperlipidemia. Current smoking was defined as active use of tobacco products at the time of enrollment into the study. To identify eligible patients to perform a treadmill EST, we inquired about the characteristics of chest pain (onset, duration, presence of resting chest pain, and associated symptoms) and carried out standard 12-lead ECG. The treadmill EST used the Bruce method and was considered positive when the patient developed significant ST-segment changes (>2 mm horizontal or downsloping depression or >1 mm elevation) in more than 2 continuous leads. After performing the EST, patients were categorized by their Duke treadmill score (DTS): low risk (DTS ≤5); intermediate risk (−10≤DTS<5); high risk (DTS ≤10). The formulation used to calculate the score was: exercise time (min)−[5×ST-segment change (mm)]−[4×angina index]. Immediately before and after the treadmill test, peripheral venous blood samples were obtained from each patient and processed within 30 min. To quantify the serum level of IMA, we used a Hitachi clinical analyzer 7180 (Hitachi, Japan) for serum samples, and the ACB Test (Ischemia Technologies). The ∆IMA, which was defined as post-EST IMA–pre-EST IMA, was calculated for all patients. According to the results of EST and ∆IMA, patients were categorized into 3 groups (none was classified as EST(−)/∆IMA(+); (1) EST(−); (2) EST(+)/∆IMA(−); and (3) EST(+)/∆IMA(+). We compared the DTS among the groups. Of the patients with EST(+), coronary angiography (CAG) was performed to evaluate the extent of CAD and patients were divided into 2 groups according to their ischemic burden: (1) large ischemic burden–left main disease, 3-vessel disease, and 2 vessel disease with significant disorder of proximal left anterior descending artery or (2) small ischemic burden–2-vessel disease without significant disorder of the proximal left anterior descending artery or single-vessel disease and non-significant irregularities. Significant stenosis on CAG was defined as ≥70% diameter stenosis, except for the left main artery, which was ≥50% diameter stenosis. All patients signed written informed consent and the protocol of the study was approved by the Institutional Review Board of Uijungbu St Mary’s Hospital.

Statistical Analysis

Results are presented as mean ± standard deviation for continuous variables and as a frequency percentage for categorical variables. Group comparisons for continuous variables were performed using ANOVA test and analysis of categorical data was performed using the Tukey’s b-test as a post-hoc t-test. The statistical analyses were performed with SPSS release 15.0 for Windows (SPSS Inc, Chicago, IL, USA). All statistical tests were 2-tailed and P<0.05 was considered statistically significant.
Results

Baseline Characteristics
Of the 155 patients, 89 were male and the mean age was 53±13 years. After the treadmill EST, 60 (38.7%) patients were determined to have a positive result and 14 (23.3%) of them showed an increase in IMA immediately after EST compared with before EST. When the patients were categorized into 3 groups according to the results of EST and the pattern of ΔIMA, there were no significant differences among the groups in age, sex, history of hypertension and smoking, blood pressure, heart rate, or lipid profile. The proportion of patients with diabetes mellitus were higher in the EST(+) group compared with EST(−) (Table 1).

Relationships Between Ischemic Burden and ΔIMA During EST

Relationship Between ΔIMA and DTS The ΔIMA had an inverted correlation with DTS (r=−0.204, P=0.011; Figure 1). When the patients were divided into groups according to the

Figure 1. Relationship between the change in ischemia-modified albumin (ΔIMA) and Duke treadmill score.

Figure 2. Comparison of Duke treadmill score according to the result of exercise stress testing (EST) and the change in ischemia-modified albumin (ΔIMA).
Usefulness of Ischemia-Modified Albumin DTS, the score was significantly lower in the EST(+) / ∆IMA(+) group compared with the other groups (−9.0±7.9, −1.7±4.2, 6.7±4.4, respectively, P<0.001; Figure 2).

Extent of CAD on CAG Of the 60 patients with EST(+), 43 (71.6%) underwent CAG and when they were divided into 2 groups according to the type of ischemic burden, ∆IMA was significantly higher in those with a large ischemic burden than in those with a small ischemic burden (−10.3±10.8 U/ml vs 0.8±14.4 U/ml, respectively, P<0.019; Figure 3). In addition, the proportion of patients with a large ischemic burden was higher in the EST(+) / ∆IMA(+) group compared with the EST(+) / ∆IMA(−) group (72.7% (8/11) vs 15.6% (5/32), P=0.001; Figure 4). The proportion of patients undergoing PCI showed an upward-trend in the EST(+) / ∆IMA(+) group compared with the EST(+) / ∆IMA(−) group (50.0% (7/14) vs 39.1% (18/46), P=0.46).

CI, confidence interval. Other abbreviations see in Table 1.

Table 2. Multiple Regression Analysis Associated With ∆IMA(+) in EST(+)

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.875</td>
<td>0.888–1.012</td>
<td>0.092</td>
</tr>
<tr>
<td>Sex</td>
<td>0.346</td>
<td>0.057–13.404</td>
<td>0.570</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.044</td>
<td>0.526–16.848</td>
<td>0.976</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.750</td>
<td>0.018–30.625</td>
<td>0.879</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.046</td>
<td>0.000–4.336</td>
<td>0.185</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>1.506</td>
<td>0.858–2.641</td>
<td>0.154</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.959</td>
<td>0.884–1.041</td>
<td>0.318</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.513</td>
<td>0.221–1.188</td>
<td>0.119</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.654</td>
<td>0.368–1.161</td>
<td>0.147</td>
</tr>
<tr>
<td>Duke treadmill score</td>
<td>1.604</td>
<td>1.031–2.495</td>
<td>0.036</td>
</tr>
</tbody>
</table>
Independent Factor Associated With Increased IMA
Multiple regression analysis revealed DTS as an independent factor related to ∆IMA(+)EST (+) (odds ratio: 1.604, 95% confidence interval: 1.031–2.495, P=0.036; Table 2).

Discussion
Several biomarkers of early myocardial ischemia in patients with chest pain have been reported.2–20 In this study, we demonstrated that an increase in IMA after EST suggests a large ischemic burden of CAD.

There are several reports about the ∆IMA during EST.21–25 Apple et al reported that the IMA concentration decreased immediately post-race compared with pre-race in 19 healthy marathon runners and they insisted that the IMA marker was not likely to be increased because of heart or acute skeletal muscle ischemia produced by significant exercise, at least in the period immediately after exercise in healthy subjects, but that increases 24–48 h post-race may be attributable to gastrointestinal ischemia or perhaps a delayed response to skeletal muscle ischemia.21 Similarly, in a study of 10 healthy volunteers, an immediate and transient decrease in IMA concentration was observed after induction of forearm ischemia by hand-grip.22 Roy et al23 also reported that IMA was significantly lower immediately after exercise-induced leg ischemia in patients with documented peripheral vascular disease and was related to disease severity. In that study, the albumin concentration did not change with exercise and no correlation was found between IMA and albumin levels at any time point, so it was proposed that this immediate decrease could be attributable to interference with IMA measurement by lactate production during exercise as a result of skeletal muscle ischemia.23–25 In 38 patients with suspected CAD who were undergoing symptom-limited exercise myocardial perfusion scintigraphy, the IMA levels were significantly lower at maximum exercise than at baseline and returned to baseline values within 1 h after stress in patients with and without ischemia.24 Recently, Sharoreuni et al25 reported a change in IMA during EST and its additive effect on the diagnostic value of EST. In that study, the serum IMA level was significantly decreased at peak exercise compared with baseline and returned to initial values after 60 min in both positive and negative EST patients, so did not seem to reflect myocardial ischemia or increase the diagnostic value of EST. They suggested that the hemocoagulation that occurs during physical exercise might induce an increase in albumin serum levels and subsequently a decrease in the unbound portion of a fixed amount of cobalt. In the present study, we found that IMA levels were significantly decreased after EST compared with baseline in patients with EST(+) ; however, among patients with EST(+), 23.3% showed an increase in IMA immediately after EST compared with before EST. We consider that the large ischemic burden in this group might have provoked active ischemia during EST, which overcame the reduction in IMA because of lactate produced in skeletal muscles and the serum albumin elevation by hemocoagulation. From this point of view, we demonstrated that DTS was significantly lower in the EST (+)/IMA (+) group compared with the other groups, and that the proportion of patients with a large ischemic burden on CAG was significantly higher in the EST (+)/IMA (+) group compared with the other groups.

There seem to be at least 2 reasons for the elevation in the IMA level during exercise in patients with severe ischemic heart disease. One is an onset of myocardial ischemia itself and the other is the impaired left ventricular wall motion induced by myocardial ischemia (ie, cardiac hibernation), because IMA is reported to change similarly to B-type natriuretic peptide.26,27

Our findings suggested that the ∆IMA during EST may have a dual role in the diagnosis of ischemic heart disease as both a useful marker of the severity of myocardial ischemia and assisting in the decision to perform PCI.

References


