Ischemia-Modified Albumin in Relation to Exercise Stress Testing

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OBJECTIVES We examined whether ischemia-modified albumin (IMA) plasma levels change during exercise stress testing (EST) in patients with known coronary artery disease and whether the induced changes differ between positive and negative exercise tests.

BACKGROUND Ischemia modified albumin is considered a marker of myocardial ischemia and increases after coronary angioplasty and in acute coronary syndromes.

METHODS We studied 40 consecutive patients with established coronary artery disease who underwent EST. Venous samples, for IMA measurement, were collected before the stress test (baseline), at peak exercise, and 60 min after the completion of the exercise test.

RESULTS There was significant difference in the IMA values at the 3 prespecified time points (p = 0.012), whereas there was no interaction between the IMA changes and the result of the stress test, whether positive or negative (p for the interaction term = 0.94). Baseline, peak EST, and post-EST IMA levels were similar in patients with positive and negative exercise tests (p = 0.61). The IMA significantly decreased at peak exercise compared with baseline values in positive (p < 0.0001) and in negative EST (p = 0.012). Moreover, IMA concentration increased 60 min after EST compared with peak-EST values in positive (p < 0.0001) and in negative tests (p = 0.003), returning to pre-EST levels in both groups.

CONCLUSIONS The IMA plasma levels change significantly during exercise testing in patients with coronary artery disease, but there is no difference between positive and negative stress tests; this possibly implies that the observed changes do not reflect myocardial ischemia.

Ischemia-modified albumin (IMA) is considered a marker of myocardial ischemia, in contrast to cardiac enzymes (creatine kinase, creatine kinase-myocardial band [MB], and troponins) that are released when cardiac necrosis occurs. Ischemia, through hypoxia, acidosis, sodium and calcium pump disruptions, and free radical injury, might induce changes in the binding capacity of the amino terminus of the albumin to bind metals such as cobalt, copper, and nickel. Ischemia modified albumin has been reported to increase after percutaneous coronary intervention (PCI) (1–4) and in acute coronary syndromes (5–7).

We examined whether the IMA plasma levels change during exercise stress testing (EST) in patients with known coronary artery disease and whether the induced changes differ between positive and negative exercise tests.

METHODS

We studied 40 consecutive patients with established coronary artery disease who underwent EST as part of their scheduled clinical follow-up; 38 were men, and 2 were women, and their age was 59 ± 9 years (range 41 to 75 years). Thirty-two patients had previous revascularization procedures—PCI or coronary artery bypass graft—and the remaining 8 had at least one >80% stenosis on angiography. Ten patients were diabetic and 24 were hypertensive; all patients underwent exercise testing while taking their medications. All patients gave written informed consent, and the study protocol was approved by the ethics committee of our hospital.

All patients performed the treadmill exercise test with the Bruce protocol. Peripheral venous samples were collected before the stress test (baseline), at peak exercise, and 60 min after the completion of the exercise test via an indwelling catheter. The blood samples were frozen at −70°C and stored until assayed. Serum IMA was measured with the albumin cobalt binding test on an Integra 800 analyzer (Roche, Rotkreuz, Switzerland). According to the manufacturer, expected values determined in a population of 283 healthy individuals range from 52 to 116 U/ml with a 95th percentile at 85 U/ml. The total interassay imprecision (coefficient variation) was 2.7% to 5.7% at 56.3 to 125.9 U/ml for quality control material. The EST was considered as positive when the patient developed significant ST-segment T-wave changes (>2 mm ST-segment horizontal or downslopping depression).

Statistical analysis. Data are presented as median values, range, and 25th and 75th percentiles. Analysis of variance with repeated measures was used to test for differences in IMA levels between time points. Furthermore, the Wilcoxon test was applied for pairwise comparisons with Bonferroni correction to account for the inflation in type I error. SPSS statistical software (SPSS Inc., Chicago, Illinois) was used in all data analyses.

RESULTS

Twenty-five exercise stress tests were positive, 14 were negative, and 1 was equivocal and was excluded from further
analysis. The IMA levels [median (25th, 75th percentile)] for all (n = 39) patients were: 82 U/ml (78, 87) at baseline, 75 U/ml (69, 81) at peak, and 85 U/ml (79, 91) 60 min after peak exercise. There was significant difference in the IMA values at the 3 prespecified time points (p = 0.012), whereas there was no interaction between the IMA changes and the result of the stress test, whether positive or negative (p for the interaction term = 0.94) (Fig. 1). The baseline, peak-EST, and post-EST IMA levels were similar in patients with positive and negative exercise test. The IMA significantly decreased at peak exercise compared with baseline values by 10% in positive (p < 0.0001) and by 8% in negative EST (p = 0.012). Moreover, IMA concentration increased 60 min after EST compared with peak-EST values by 15% in positive (p < 0.0001) and by 13% in negative tests (p = 0.003), returning to pre-EST levels in both groups. A highly significant U-shape trend was observed regarding IMA levels before, at peak, and after EST (p for parapabolic trend <0.001). In addition, IMA concentrations did not differ between the 2 groups (positive and negative) at any of the time points (p = 0.61).

**DISCUSSION**

We found that IMA plasma levels significantly decrease at peak exercise compared with baseline and return to initial values after 60 min; this occurs similarly in both positive and negative exercise tests; therefore, it does not seem to reflect myocardial ischemia and does not increase the diagnostic value of EST.

Our results confirm those of a previous report (8) that had investigated IMA kinetics in 38 patients with chest pain and suspected coronary artery disease undergoing single-proton emission computed tomography imaging. In that study, IMA levels were also significantly lower at maximum exercise than baseline and returned to baseline values within 1 h after stress; this occurred in patients with and without ischemia. Furthermore, IMA levels were similar between the 2 groups at all time points of the protocol—before exercise; at maximum exercise; and 1, 2, 3, 4, 5, and 6 h after exercise. Interestingly, in the same study albumin plasma levels were also evaluated and found to increase at maximum exercise, in correlation with IMA decrease, in all patients with and without ischemia. Therefore, it seems that the hemoconcentration that occurs during physical exercise induces an increase in albumin plasma levels and subsequently a decrease in the nonbound portion of a fixed amount of cobalt. The IMA concentration has also been shown to decrease immediately post-race compared with pre-race in 19 healthy marathon runners (9). Ischemia-modified albumin has been evaluated in healthy subjects after hand-grip and found to decrease significantly at 1, 3, and 5 min after forearm ischemia and return to baseline thereafter. The same changes were reported for IMA/albumin ratio (10). Likewise, in patients with documented peripheral vascular disease undergoing claudication, limited treadmill test IMA decreased significantly compared with baseline and returned to baseline at 1 h after stress, although in this study albumin concentration did not change with exercise and no correlation was found between IMA and albumin levels at any time point (11). In addition, in the same study all patients were evaluated with dobutamine stress echocardiography, which was negative in all; IMA levels were unchanged at baseline, peak stress, and 1 h after stress, unlike our negative exercise tests where IMA changed significantly and similarly to our positive stress tests. Still, one should also take into account that myocardial ischemia during stress test—either physical or pharmacological—might not be as severe as the ischemia that occurs during PCI or in the acute coronary syndrome setting. Because in the latter 2 conditions IMA increases (1−7), it is intriguing that its levels decrease in EST−induced ischemia, as found in our and other studies. Although speculative, it seems that during EST−induced ischemia, 2 different mechanisms might influence IMA levels; active ischemia tends to increase IMA, but eventually the hemoconcentration mechanism predominates, resulting in decreased IMA concentration.

We conclude that IMA plasma levels change significantly during exercise testing in patients with coronary artery disease, but there is no difference between positive and negative stress test; this might imply that the observed
changes do not reflect myocardial ischemia. The IMA measurement does not seem to improve the accuracy of EST.

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