Biomarkers in ischemic cardiac syndromes

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Chapter 8

Ischemia-modified albumin measurements in symptom-limited exercise myocardial perfusion scintigraphy reflect serum albumin concentrations but not myocardial ischemia

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Introduction

The albumin cobalt-binding (ACB) test (Ischemia Technologies), which measures the concentration of ischemia-modified albumin (IMA), has been cleared by the US Food and Drug Administration for use as a rule-out marker for acute myocardial ischemia (1). The test is based on the reduced capacity of human albumin to bind cobalt as a result of structural changes in the NH2 terminus of the albumin molecule in conditions of myocardial ischemia (2,3). Moreover, IMA concentrations correlated with disease severity in systemic sclerosis (4), and an exercise-induced decrease in IMA concentrations correlated with the ankle-brachial index in patients with peripheral artery sclerosis (5). Little is known, however, about the relationship between exercise-induced myocardial ischemia, albumin kinetics, and IMA kinetics. We therefore investigated this relationship in 38 patients with chest complaints and suspected coronary artery disease who were undergoing symptom-limited exercise myocardial perfusion scintigraphy.

Methods

Myocardial perfusion scintigraphy was performed according to the guidelines of the American Society of Nuclear Cardiology (6), with a 2-day stress/rest protocol. A dose of 500 MBq of [99mTc]-Tetrofosmin was administered at rest and at peak exercise. Electrocardiogram-gated single photon emission tomography imaging was started 45 min to 1 h after the administration of radioactive-labeled tracer. All patients exercised on a bicycle ergometer with a starting workload of 50 W, increasing every 2 min by 25 W. Endpoints for exercise included achievement of at least 85% of the age-predicted heart rate, recognizable chest pain, and a > 2-mm ST-segment depression (7). All patients fasted both days. All antianginal medication was discontinued for at least 48 h before the exercise test and restarted immediately after exercise. Stress and rest perfusion images were scored in consensus by two experienced nuclear medicine physicians (H.J.V. and B.L.F.V.E.S.), who used a 5-point semiquantitative score for each of 17 myocardial segments. Perfusion defect severity was classified as normal (0), equivocal abnormal (1), mildly abnormal (2), moderately abnormal (3), or severely abnormal (4). The summed stress score (SSS), summed rest score (SRS), and the difference between those scores [summed difference score (SDS)] were then calculated. Improvement at rest of one or more grades was considered to be a “reversible” perfusion defect if present in more than one adjacent segment. An SDS ≥ 3 was considered to indicate clinically relevant ischemia. Estimates of left ventricle ejection fraction (LVEF) were calculated by use of a completely automated algorithm that has been described previously and validated (8,9). On the day of the symptom-limited exercise test, serum samples were drawn before exercise, at maximum exercise, and 1, 2, 3, 4, 5, and 6 h after exercise; all samples were then frozen at -80 °C until analysis. A Roche Diagnostics Modular P-800 instrument was used for spectrophotometric measurement of IMA (ACB test; Ischemia Technologies), turbidimetric
measurement of serum IgM (Tina Quant, IgM gen 2; Roche Diagnostics), and photometric measurement of serum creatinine (Crea plus; Roche Diagnostics) and albumin (Tina Quant; Roche Diagnostics). Creatinine clearance was calculated by use of the Cockcroft–Gault formula. The χ² test was used to compare dichotomous variables. Continuous variables were compared between groups with the Student t-test or Mann–Whitney U-test as appropriate. The Spearman rank correlation test was used to assess the relationship between non-gaussian-distributed continuous variables, and stepwise linear regression analysis was used for multivariate analysis of continuous variables. P values < 0.05 were considered to indicate statistically significant differences except for multivariate analysis, for which a P value < 0.1 was considered to indicate statistically significant differences. The study was approved by the medical ethics committee.

Results

Of 38 patients studied, 15 had ischemia on myocardial perfusion scintigraphy. Ischemia patients [SDS = 6 (interquartile range, 5–10)] had a higher incidence of documented coronary artery disease and had higher nitrate and statin use than did patients without myocardial ischemia. When we compared results for patients with ischemia vs those without ischemia, we found no differences in male sex [12 (80%) vs 17 (74%); P = 0.67], age [median (interquartile range), 59 (52–72) vs 61 (55–71) years; P = 0.96], SRS [4 (0–11) vs 2 (0–7); P = 0.42], LVEF [51 (47–59)% vs 59 (52–65)%; P = 0.14], creatinine clearance [96 (90–125) vs 87 (75–106) mL/min; P = 0.24], and baseline concentrations of albumin [42 (41–46) vs 43 (41–45) g/L; P = 0.66], IgM [0.83 (0.61–1.23) vs 1.00 (0.64–1.40) g/L; P = 0.41], and IMA [99 (92–106) vs 97 (92–104) kilounits/L; P = 0.48]. Baseline IMA concentrations were associated with LVEF (r = -0.538; P = 0.001) and albumin [IMA (kilounits/L) = -2.36 X albumin (g/L) + 200 kilounits/L; r = -0.831; P < 0.001; figure 1A], but not with any other clinical or biochemical characteristics. Multivariate linear regression analysis showed that the albumin concentration was the only independent predictor of IMA concentration (P < 0.001; adjusted r² = 0.776). The relative changes in IMA for patients with or without myocardial ischemia are shown in figure 1B. Absolute and relative concentrations of both IMA and albumin did not differ between the groups at any of the time points. At maximum exercise, patients from both groups had IMA concentrations significantly lower than baseline values [median (interquartile range), 98 (92–105) kilounits/L for non-ischemic patients and 81 (74–88) kilounits/L for ischemic patients; P < 0.001] and significantly higher albumin [43 (41–45) and 46 (44–49) g/L; P < 0.001] and IgM [as an indicator of water shift across the vessel wall during exercise; 0.84 (0.62–1.35) and 0.94 (0.69–1.51) g/L; P < 0.001] concentrations. The absolute change in IMA correlated with the absolute change in albumin (r = 0.484; P = 0.002) and IgM (r = 0.369; P = 0.027) concentrations. Multivariate linear regression analysis showed that the absolute increase in albumin concentration was the only independent predictor of absolute decrease in IMA (P = 0.003; adjusted r’ = 0.204).
Figure 1. Correlation between baseline concentrations of albumin and IMA (A), and mean (SD; error bars) relative changes in IMA (B). (B), dotted line, patients with ischemia; solid line, patients without ischemia.
Discussion

Physical exercise causes hemoconcentration, with subsequent increases in concentrations of plasma proteins, such as albumin (10). In a population of persons with suspected myocardial ischemia, we found that IMA, measured by the ACB test, which quantifies the nonbound portion of a fixed amount of cobalt added to albumin in the sample, is specifically dependent on the concentration of serum albumin and does not reflect the presence of myocardial ischemia. Although proponents of the test argued that IMA is a useful diagnostic tool insensitive to albumin concentrations (1), the correlation between IMA and albumin in our study was highly comparable to that found by others (11). Furthermore, the decrease in IMA concentrations after short exercise has also been reported after long-time exercise (i.e., after marathon running) (12). Previous results on the diagnostic value of high IMA concentrations in patients with chest pain (13–17) are, at least partly, attributable to the dependency of IMA on albumin, as low albumin concentrations are associated with a higher risk for adverse cardiac events.
References


