Brief Communications

Ischaemia modified albumin: Does it bolster our diagnostic ammunition?

INTRODUCTION

Although cardiac troponin (cTn) and creatine kinase-muscle type and brain type (CK-MB) are sensitive and specific for the detection of myocardial damage, they may not rise during reversible myocardial ischaemia; and in acute coronary syndrome (ACS), they may take up to 4 hours to get elevated. Hence, there is a need for a marker that can possibly overcome these lacunae. Ischaemia-modified albumin (IMA) has higher sensitivity (than cTn, CK-MB and myoglobin) during the early phase of ACS, and can be an ideal marker in the early diagnosis of ACS. It is hypothesized (and supported in *in vitro* experiments) that reactive oxygen species like superoxide and hydroxyl radicals generated during ischaemia–reperfusion modify the N-terminus of human serum albumin (HSA), especially at the *N*-Asp-Ala-His-Lys sequence resulting in IMA formation with albumin acting as a "sacrificial" antioxidant to reduce the injury during reperfusion.[1] The commonly used diagnostic test-albumin cobalt binding (ACB) test detects the reduction in the affinity of serum albumin for cobalt. The compensatory hyperadrenergic state during myocardial ischaemia causes the rise in plasma concentrations of free fatty acids (FFA) and the corresponding FFA-induced conformational perturbations of HSA form the basis of the IMA test. The increased lactate level in post-ischaemic state causes interference in IMA measurement and is another factor attributed to the rise in IMA. IMA has been cleared by the US Food and Drug Administration as a biomarker to exclude myocardial ischaemia.

EVIDENCE FOR EFFICACY

Cardiac setting

The elevation of IMA after a percutaneous coronary intervention is associated with higher target lesion revascularization.[2] In a study, sensitivity of IMA at presentation for an ischaemic-origin chest pain was 82%, compared with 45% of ECG and 20% of cardiac troponin type T (cTnT). IMA used together with cTnT or ECG, had a sensitivity of 90% and 92%, respectively. All the three tests combined, identified 95% of patients whose chest pain was attributable to ischaemic heart disease.[3] A meta-analysis spanning more than 1800 patients concluded that combining negative electrocardiogram (ECG) changes, negative troponin and negative IMA significantly increased the sensitivity and negative predictive value (NPV) to 94.4% and 97.1% for excluding ACS, and to 89.2% and 94.5% for longer term outcomes, respectively.[4] In patients with unstable angina, sensitivity of IMA used alone was equivalent to that of IMA and ECG combined.

The use of calculated albumin-adjusted IMA index [IMA index = serum albumin concentration (g/dl) × 23 + IMA (U/ml) − 100] heightens the sensitivity of ACS diagnosis.[5] IMA (at levels >93.3 U/ml) is an independent predictor of both 30-day combined end point (cardiac death, myocardial infarction, recurrent angina) and 1-year mortality in patients presenting to the emergency room (ER) with typical acute chest pain.[6]

Melatonin is theorized to exert a beneficial effect as a radical scavenger in myocardial ischaemia–reperfusion. Patients with segment elevation myocardial infarction (STEMI) showed a diurnal fluctuation in IMA, with significantly higher levels at 2:00 am. An inverse correlation (statistically significant) was found between IMA and melatonin at 2:00 am and at 9:00 am, after adjustment for cardiovascular risk factors.[7]

In patients with acute myocardial infarction-AMI (enrolled in the French Nationwide OPERA study), 40% of patients in the highest IMA quartile measured within 24 hours (>104 IU/ml) reached the end point (death, resuscitated cardiac arrest, recurrent myocardial infarction or ischaemia, heart failure, stroke) compared with 20% in the lowest (<83 IU/ml) by 1 year. Plasma IMA, brain natriuretic peptide, heart failure and age are noted to independently predict a composite end point at 1 year.[8]

In 52 in- or out-of-hospital cardiac arrest patients, compared with healthy controls, IMA measured at the beginning or within 5 min of commencement of cardio-pulmonary resuscitation (CPR), showed a sensitivity of 65.8% and specificity of 78.6% (positive predictive value-85.3% and NPV- 45.8%) at an optimum cut-off point of 0.235 absorbance units (ABSU).[9]

Serum levels of IMA get significantly elevated in the

ACS and reach peak at 2 h after onset of chest pain and start returning to baseline at 6 h. Serum levels of myoglobin start to elevate at 2-4 h after chest pain onset, while CK-MB and cardiac troponin type l (cTnI) start rising 4-6 h after chest pain onset. In a retrospective study of the patients diagnosed with ACS following ER presentation with acute chest pain, the correct diagnosis rate was significantly higher as determined by assessment of IMA (81.02%) vs. cTnI (42.34%) within 3 h of ER presentation.[10]

ST segment resolution (STR) also correlates with IMA. Serum IMA concentrations were significantly higher in patients that had incomplete STR [worst single ECG lead before and 90 min after primary percutaneous coronary intervention (PCI) graded according to the degree of STR: Complete (≥70%) or incomplete (<70%)]. It showed a sensitivity of 91.4% and a specificity of 45.7% for the diagnosis of incomplete STR and independently predicted incomplete STR even after adjustment for potential confounders.[11]

IMA concentration is higher in unstable angina (UA) patients than in stable angina (SA) patients or healthy controls. IMA negatively correlates with left ventricular ejection fraction (LVEF) in UA patients and increases significantly in patients with an abnormal LVEF (<50%), compared with those with a normal LVEF (≥50%).[12] IMA levels obtained at admission are powerful indicators of short-term (30 day) mortality in STEMI patients treated with primary PCI.[13]

The serum levels of IMA in those with acute myocardial infarction (AMI) at 2, 4 and 6 hours after the onset are significantly higher than that in normal controls.

NPV for early diagnosis of acute coronary ischaemia of IMA and C-reactive protein (CRP) for ischaemia origin was 79.2% and 38.6%, respectively.[14] In another study IMA, high sensitivity C-reactive protein (hsCRP) and N-terminal proBNP (brain natriuretic peptide) were higher, while total antioxidant status (TAS) was lower in coronary artery disease (CAD) patients than in controls (statistically significant), and IMA and TAS negatively correlated in all subjects. IMA did not correlate with the number of diseased vessels. For CAD diagnosis, the best cut-off point for IMA was 101.5 KU/l with sensitivity and specificity of 87.7% and NPV of 83.3%.[15] IMA determination may provide earlier information of CAD presence before hsCRP or NT-proBNP elevation, contributing to the early assessment of overall patient risk.

IMA in non-cardiac scenario

In a study, plasma IMA levels in patients diagnosed of pulmonary embolism (PE), 97.7% had values exceeding 0.540 ABSU, compared to none in the control group.[16] In an animal model, PE with/without deep venous thrombosis showed statistically significant elevations of IMA at 0, 1, 3 and 6 hours. Being 100-200 times less expensive than D-dimer, IMA thus has a lot of potential in the diagnosis of PE.[17]

In thromboembolic occlusion of superior mesenteric artery, statistically significant increases in IMA were observed (0.264±0.057 ABSU, compared to 0.163±0.025 ABSU in the control group).[18] Another animal study proved the same with rising plasma IMA levels in mesenteric artery occlusion (6 hours post-ischaemia higher than 2 hours and 30 min) compared to controls.[19] Coupled with high index of clinical suspicion, IMA certainly has a role in diagnosing mesenteric ischaemia.

IMA may be a biomarker for early identification of acute stroke. A study on 118 patients presenting within 3 h of the onset of an acute neurological deficit (84 brain infarctions [BI]) concluded that during the first 24 h, IMA levels significantly increased in BI patients.[20]

IMA is shown to be elevated in diabetic patients. Diabetics with poor glycaemic control have higher IMA level, compared to those with good glycaemic control. Significant correlation exists between IMA and HbA1c (weak association with blood pressure). In a study, fasting glucose, glycated albumin, triglycerides, creatinine, IMA and hs-CRP were significantly higher in patients with type 2 diabetes. Weak, but significant correlations were seen between IMA and fasting glucose and IMA and hs-CRP.[21] Significant correlations between IMA and total cholesterol, LDL cholesterol, oxidized low-density lipoprotein (ox-LDL) antibodies and hs-CRP levels have also been noted.[22] Hyperglycaemia, hypercholesterolemia and inflammation via oxidative stress and chronic hypoxia may modify albumin and hinder its capacity to bind cobalt, resulting in higher IMA levels. IMA formation is noted to be associated with oxidative stress and atheromatous plaque development.

A study reported that both IMA and IMA/alb were significantly elevated during pre-eclampsia up to delivery, compared with healthy pregnant women.[23] Median first trimester serum IMA concentrations

are significantly higher in women who subsequently developed pre-eclampsia (median 126.5 kU/l) when compared to those with normal pregnancy outcome.[24] This rise in IMA may be a clinical manifestation of abnormally high intrauterine hypoxia and subsequent reperfusion oxidative damage that underlie defective endovascular trophoblast development. First trimester serum IMA may thus be a potential biomarker for abnormal placental development.

Elevated serum IMA levels are observed in ovarian torsion and may point to the early diagnosis. It also correlates with follicular cell degeneration, vascular congestion, haemorrhage and inflammatory cell infiltration seen in ovarian torsion.[25]

A high level of IMA is observed in carbon monoxide (CO)-poisoned patients, owing to its sensitivity to hypoxia, although, further investigations are needed to establish the association.[26]

Elevations of IMA have also been noted in anaemia in chronic kidney disease. In end stage renal disease, elevated levels of IMA correlated with larger left ventricular (LV) size, decreased systolic function and greater estimated LV filling pressures.[27]

Weaker evidence

In a study, the correlation of IMA and heart-type fatty acid binding protein (h-FABP) with non-ST-segment elevation ACS was researched among 677 patients admitted to the ED with chest pain. While IMA was not predictive of the non-ST-segment elevation, ACS diagnosis (IMA level was higher than 85 U/ml both in the ACS and in the non-ischaemic chest pain), h-FABP predicted ACS diagnosis with specificity at 96.8% and sensitivity at 13.5%.[28] These results corroborate the findings of the presentation of ischaemia-modified albumin in ER (PRIMA) study that the diagnostic accuracy of IMA does not support its use as an effective risk stratification tool for patients admitted with chest pain to the ED. Lower sensitivity, lower NPV and narrow diagnostic time window have been blamed for the non-reliance on IMA. Although plasma IMA levels change during pharmacologic stress testing, in patients with CAD, there is no significant difference between the positive and the negative tests.[29] Some researchers believe that they might not actually reflect myocardial ischaemia. Other hypotheses state that the release of IMA may depend on reperfusion-induced events rather than ischaemia per se.

In a study, the sensitivity of admission IMA (at optimal cutoff threshold −91 U/ml) for a final diagnosis of ACS was 86%, specificity −49%, and NPV 88%. But, IMA did not provide superior sensitivity or specificity at any time compared with other biomarkers (cTnT, CK-MB mass, myoglobin and h-FABP).[30]

CONCLUSION

As a stand-alone marker, IMA does not seem to have bolstering evidence in its potential to diagnose ACS, but as an adjuvant to the other markers and modalities, it may significantly amplify the sensitivity, specificity and NPV in early detection of myocardial ischaemia. Further, large randomized control studies are warranted to delineate its stand in the same.

ACKNOWLEDGEMENT

We thank our colleagues and staff of Cardiology and Internal medicine.

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DOI: 10.4103/0019-5049.84840