Review Article

Ischemia Modified Albumin: Is This Marker of Ischemia Ready for Prime Time Use?

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Acute coronary syndromes (ACS) represent a continuum of disease ranging from unstable angina, associated with reversible myocardial cell injury, to ST-segment elevation myocardial infarction, associated with irreversible myocardial necrosis. The common pathophysiological feature of the ACS spectrum is the rupture or erosion of atheromatous plaque.[1,2] A number of cardiac biomarkers have been described that detect different stages in the development of ACS.[3,4] The use of these biomarkers can be divided into two categories: diagnosis and risk stratification. From a diagnostic standpoint, the aim is to try and develop biomarkers that identify patients with ACS, even when there is no evidence of myocyte necrosis. Patients with cardiac ischemia are at increased risk for subsequent coronary events but they may often be discharged because there is insufficient evidence to justify hospital admission. In cases with cardiac ischemia, rather than necrosis, it may be more difficult to confirm the diagnosis when the patient has acute chest pain, non-diagnostic electrocardiograms (ECG), and normal biomarkers for necrosis. This diagnostic target is still in its infancy and there is no "gold standard" for accurately assessing myocardial ischemia.

Although a number of new cardiac marker strategies (e.g. free fatty acids, choline)[3] have been developed with the potential of improving the diagnosis and treatment of patients with possible ACS, to date only one clinical test for ischemia has received approval from the US Food and Drug Administration: ischemia modified albumin (IMA).[5]

Physiology and IMA assay

First identified in the early 1990s, IMA is produced when ischemia stresses released from hypoxic heart tissue induce modification of circulating albumin.[5,6] The amino terminal end (N-terminal) of the albumin molecule is a binding site for transitional metals such as cobalt, copper and nickel.[4] During ischemia, the N-terminus of albumin is altered, possibly as the result of hypoxia, acidosis, free-radical injury and energy-dependent membrane disruption, decreasing its binding capacity for metals.[7,8] Increased amounts of IMA result in less cobalt binding and more residual unbound cobalt available for complex with a chromogen (dithiothreitol), which can be measured photometrically. This is the basis of the albumin cobalt-binding (ACB) test. An increase in IMA is inversely related to the unbound amount of cobalt, causing an increase in coloured product produced in the test platform (Figure 1). Blood samples need to be analyzed rapidly, avoiding sam-

ple dilutions, or can be frozen at below -20° C or lower for an indefinite period of time. This assay is reported to be positive within 6 to 10 minutes of ischemia and remains so until up to 6 hours later, allowing detection before the development of myocardial necrosis (as evidenced by normal levels of creatine kinase [CK-MB], troponin and myoglobin).[9,10] Regarding IMA clearance, the changes to albumin may not be irreversible. Thus, the rapid return to normal within a few hours (12 to 24 hours) may be a function of a return to pre-ischemic conditions with the removal of the free radicals, or an accelerated clearance due to a conformational change to the protein.[9,10]

Clinical interpretation of IMA concentrations

Reference values of IMA were determined from a population of 283 healthy individuals and ranged from 52 to 116 kilounits/L, with a 95th percentile at 85 kilounits/L (Cobas Mira).[11] While the optimum cutoff for IMA for ruling out ACS is 85 kilounits/L, the manufacturer has suggested a higher value of 100 kilounits/L for risk stratification. IMA is normally distributed in a group of apparently healthy volunteers and is not correlated with smoking, age, race, gender, or Framingham risk score.

IMA is not specific for cardiac ischemia. IMA is also elevated in most patients with liver cirrhosis, acute infections and advanced cancers; all these conditions are potent producers of free radicals. IMA seems to be produced in patients with brain ischemia (stroke), end-stage renal disease and intrauterine ischemia.[12,13] Data exist suggesting that very low albumin levels and the presence of co-existing lactic acidosis might affect assay performance.[14,15] Additional data are needed to clarify the impact of total albumin alterations on IMA interpretation.

Moreover, the ACB test is an indirect measure of IMA and such albumin has not yet been isolated.[16] An immunochemical assay, which would improve the analytical sensitivity of the test but might not have an impact on the clinical specificity, has not yet been developed.

Clinical applications of IMA

IMA as a marker of supply ischemia

The detection of ischemia prior to infarction is a challenging concept. It would be very helpful to be able to identify quickly and accurately which patients really have myocardial ischemia and may be in need of either treatment or intervention to prevent subsequent events. IMA has performed reasonably well in clinical trials focusing on its capability for early measurement to characterize ACS patients (Figure 2).

Blood levels of IMA rise promptly during myocardial ischemia triggered by a primary reduction of blood flow (supply ischemia), as seen in patients undergoing percutaneous coronary intervention (PCI), stay elevated for about 6 hours and return to baseline within 12 hours.[17-19] In a previous report, IMA production was

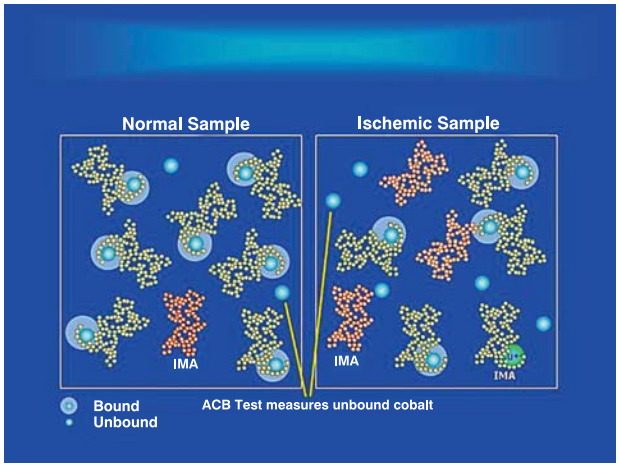

Figure 1. The albumin cobalt binding (ACB) test: an indirect measure of ischemia-modified album (IMA). In the ischemic sample, an increase in IMA is related to the unbound amount of cobalt.

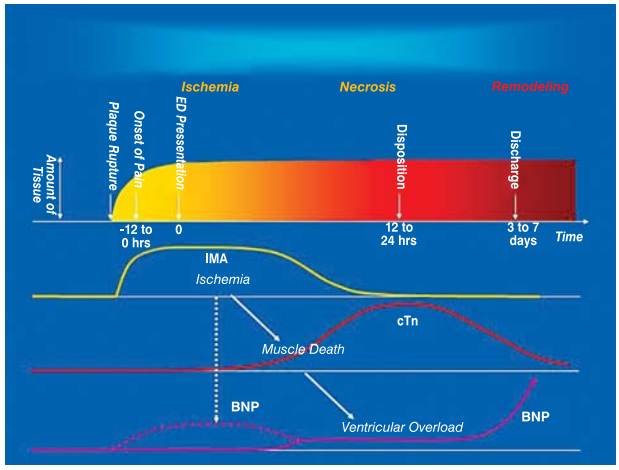

Figure 2. Acute coronary syndromes: sequence and timing.

decreased in patients with collateral vessels, which is likely to be a protective effect of collateral circulation against PCI-induced myocardial ischemia-reperfusion injury.[18] However, IMA levels during balloon angioplasty are related to the number, pressure, and duration of inflations, suggesting that IMA reflects the magnitude and duration of ischemia during PCI and may not be just a simple marker of free radical damage.[19] Several studies have also shown a good correlation between objective markers of ischemia, such as lactate levels and isoprostane concentrations, and IMA levels in this setting.[10,19] Moreover, IMA was shown to increase significantly in patients undergoing intracoronary ergonovine spasm provocation test and may have a role as a biochemical marker for transient myocardial ischemia induced by coronary vasospasm.[20]

Many studies have evaluated the clinical utility of IMA in patients presenting to the Emergency Department with suspected ACS.[21-26] In one of the first studies, Christenson et al enrolled 256 ACS patients at four centres and examined samples taken on admission and 6-24 hours later.[21] All patients had a negative cardiac troponin I (cTn-I) result at presentation and cTn-I was used as the outcome measure. At the optimum cutoff point of 75 units/mL, the sensitivity and specificity of the ACB Test were 83% and 69%, respectively. The negative predictive value was 96% and the positive predictive value was 33%. Sinha et al also evaluated IMA for the diagnosis of cardiac ischemia in 208 patients attending the Emergency Department within 3 hours of the onset of chest pain.[22] In this study, the final diagnosis was based on the history, clinical examination, serial cardiac troponin T (cTn-T) results, and data from medical records. The sensitivity of IMA at presentation for an ischemic origin of chest pain was 82%, the specificity was 46%, the negative predictive value was 59%, and the positive predictive value was 72%. Furthermore, IMA had a higher sensitivity than the 12-lead ECG and initial cTn-T levels for the diagnosis of ACS, whereas the combination of ECG, cTn-T and IMA identified 95% of patients whose chest pain was attributable to ischemic heart disease.[22] Similarly, a prospective observational study assessing low risk patients with chest pain showed that the measurement of IMA and cTn-I at presentation had high sensitivity rates (97.6%) but markedly lower specificity rates (13.6%).[23] A subsequent study of 538 patients admitted to a chest pain evaluation unit found admission measurement of IMA plus cTn-T had 100% sensitivity for prediction of a final diagnosis of acute myocardial infarction.[24] A meta-analysis of current data has shown that when the IMA result is used alone it has a 91% negative predictive value for excluding ACS in the Emergency Department, which increases to 97% when it is used in combination with negative cTn-T measurements and a normal or non-diagnostic ECG.[25] A large multicenter randomised controlled trial examining the value of IMA for chest pain evaluation is about to be launched (the IMAGINE study). This will provide a definitive answer.

However, as promising as the IMA assay appears some degree of caution is still indicated. The currently accepted strength of IMA lies in its negative predictive value for excluding the presence of ischemia. Unfortunately, predictive values cannot necessarily be translated into clinical practice; in reality, predictive value is less a measure of test performance than it is a reflection of disease prevalence in the population being tested. It is a basic principle of diagnostic testing that adding tests together increases sensitivity. Thus, adding IMA to traditional markers will increase sensitivity, but so would adding other biomarkers. In this manner, specificity will be reduced, leading to an even higher false-positive testing rate.

Nevertheless, IMA currently remains the only ischemia assay to have reached the clinical validation stage. For efficient provision of care in the Emergency Department, a high negative predictive value may be critical, because the correct exclusion of ACS preserves limited and expensive resources, such as stress tests, hospital beds and catheterization slots.[26]

IMA as a marker of demand ischemia

A number of studies have demonstrated that exercise may induce perturbations in circulating IMA levels.[27-34]

The IMA concentration has been shown to decrease immediately post race followed by an elevation 24-48 hours post exercise in 19 healthy marathon runners.[28] Similar findings were confirmed by additional reports assessing IMA levels in healthy individuals following completion of high workload exercise.[29] The IMA has also been evaluated in healthy subjects following hand grip and was found to decrease significantly after forearm ischemia and to return to baseline thereafter; similar changes were reported for the IMA:albumin ratio.[15] However, Falkensammer et al recently reported a significant increase in circulating IMA concentrations in 12 healthy volunteers after exercise-

induced calf-muscle ischemia.[30] In the same study a significant negative correlation was found between IMA and albumin, but no association of IMA levels with lactate was observed.[30]

Likewise, in patients with documented peripheral vascular disease undergoing a claudication-limited treadmill test IMA decreased significantly compared to baseline and returned to baseline at 1 hour post 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.[31] In addition, in the same study, all patients were evaluated with dobutamine stress echo, which was negative in all; IMA levels were unchanged at baseline, peak stress and 1 hour after stress.[31]

In 38 patients with chest pain and suspected coronary artery disease undergoing SPECT imaging, IMA levels were also significantly lower at maximum exercise than at baseline and returned to baseline values within an hour after stress; this occurred in patients with and without ischemia.[32] Interestingly, in the same study albumin plasma levels were also evaluated and were found to increase at maximum exercise, in correlation with IMA decrease, in all patients with and without ischemia.[32] These results were confirmed by our own study, which has also demonstrated post-exercise reduction in mean IMA, and this reduction was similar for both positive and negative exercise tests of patients with known coronary artery disease.[33] On the other hand, Kurz et al have shown that IMA levels rose significantly after 4 hours in patients with and without reversible perfusion defects.[34]

It is clear that there is no homogeneous response in exercise-induced changes of IMA. Exercise results in a number of potential ischemic sites, such as skeletal muscle or gastrointestinal tract. It seems that the hemoconcentration that occurs during physical exercise induces an increase in albumin plasma levels and, consequently, a decrease in the non-bound portion of a fixed amount of cobalt. Still one should also take into account that myocardial ischemia during a stress test may be different in either physical or pharmacological stress and may not be as severe as the ischemia that occurs during angioplasty or in the ACS settings. Lactic acidosis can also interfere with the analysis of IMA as there is a negative correlation between them. Therefore, significant caution is advised in the interpretation of post-exercise IMA data.

The mechanism for detectable transient changes of IMA in response to demand ischemia requires elucidation. To date, there is no approval for use of this test in conjunction with a stress test. Clinical assessment of IMA after ischemic exercise requires standardized protocols and sampling time points and similar study populations.

IMA as a marker of myocardial injury

IMA has been evaluated as a potential indicator of transient myocardial ischemia in different clinical models of myocardial injury. Radiofrequency (RF) catheter ablation is a widely used treatment for cardiac arrhythmias but results in a detectable injury to the myocardium, which is unrelated to ischemia-reperfusion injury *per se*.[35] Moreover, any changes in IMA in association with RF ablation cannot be attributed to albumin variations because albumin levels are not expected to vary in relation to this procedure.

Our group found that IMA plasma levels did not change immediately after, 2 and 20 hours after RF ablation compared to baseline values, whereas CK, CK-MB and troponin I increased significantly compared to baseline.[36] However, a previous report on IMA in RF ablation showed that IMA significantly increased 30 min after the procedure and returned to baseline values in 8 hours.[37] The different timing may explain the contradiction between the latter study's findings and ours, although the effects of ischemia on the N-terminal region of albumin can be detectable up to 6 hours after the ischemic event.

There is one study reporting that IMA plasma levels increase 1 and 6 hours following cardioversion in patients with AF, along with an increase of CK and CK-MB;[38] it may be that cardioversion produces skeletal damage at the proximal site of shock applications, along with cardiac ischemia in the more distal cardiac tissues.

Transvenous lead implantation of either permanent pacemakers or defibrillators induces minimal myocardial injury, expressed as a rise in cardiac troponins, which are very sensitive and specific markers of myocardial cell necrosis.[35] We found that IMA and CK increased at 6 and 48 hours after permanent pacemaker/defibrillator implantation compared to baseline values, whereas CK-MB and troponin I increased at 6 hours and returned to baseline at 48 hours.[39] These data suggest that insertion of endocardial leads is accompanied in most patients by minimal necrosis. This seems to be preceded by transient ischemia, as shown by a significant increase in IMA levels, which could be attributed to myocardial ischemia. Despite the lack of

evidence in the aforementioned clinical situations, it could be speculated that the underlying mechanism may be the damage to the N-terminus by reactive oxygen species or disruption at the cellular level.

Recently, IMA has been described as a useful discriminative marker to exclude pulmonary embolism, which is known to be associated with right ventricular dysfunction and myocardial ischemia.[40] The serum IMA levels of 30 patients with definitively diagnosed pulmonary embolism were significantly higher than those of 30 healthy volunteers.[40]

Prognostic value of IMA

In the early hours of ACS, selection of patients who are at high risk for cardiac events is an important factor in determining the appropriate treatment strategy. The use of serum IMA concentrations for the early prediction of adverse clinical outcomes in patients with suspected ACS has only recently been the subject of investigation, but shows controversial results. Worster et al enrolled 189 patients who presented to an Emergency Department within 6 hours after chest pain, seeing an emergency physician who ordered a cTn-I test, and who had no serious cardiac outcome before the troponin result became available.[41] Of the 189 patients, 24 had a serious cardiac outcome within 72 hours after their arrival at the Emergency Department. The likelihood ratios for IMA measurement within 6 hours after chest pain predicting a serious cardiac outcome within the next 72 hours were 1.35 (95% confidence interval [CI] 0.315-5.79) for IMA≤80 Units/mL and 0.98 (95% CI 0.86-1.11) for IMA>80 Units/ mL.[41] Although these data suggest that IMA is a poor predictor of serious cardiac outcomes in the short term, they may be explained by taking into account the following:

1. IMA elevation is non-specific and hence may attenuate any prognostic significance if it is used for prognosis before first establishing the diagnosis. More recently, Dusek et al studied 60 patients who underwent successful elective single-vessel PCI for the management of stable angina pectoris.[42] Post-PCI IMA elevation more than 130 kilounits/L was associated with higher target lesion revascularization at nearly 4-years follow-up (p=0.026).[42] Interestingly, in patients with ST-segment elevation myocardial infarction treated with PCI and who developed heart failure, IMA levels were significantly associated with a decreased left ventricular ejection fraction, representing an early marker of left ventricular dysfunction.[43]

2. IMA levels vary considerably, even among healthy individuals, and taking these variations into account may improve the predictive characteristics of IMA. Aparci et al have also investigated the prognostic significance of IMA in patients with ACS. IMA was found to be significantly related to 1-year mortality but with a cut-off value of 477 Units/mL.[44]

The prognostic significance of IMA needs be evaluated in large populations and randomised study groups before it can be used for risk stratification in patients with ACS.

Conclusions

The remarkable increase in the discovery of new biomarkers demands great attention to their assessment before clinical application. The value of IMA lies in its negative predictive value for excluding the presence of ischemia in a population with a low prevalence of coronary artery disease. Rather than providing evidence of ischemia, perhaps its greatest role will be reassurance. Although, this marker is not very specific, it is highly sensitive when negative. It is interesting to note that an elevated IMA also appears to be an outcome predictor. Before changing clinical practice, meaningful studies addressing utility, outcomes and cost-effectiveness need to be conducted.

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