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Role of ischemia-modified albumin in clinical practice

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Abstract: Difficulty in establishing a diagnosis of acute coronary syndrome (ACS) in the clinical setting has led researchers to investigate novel markers that show increased blood levels before the myocardial necrosis occurs. In ischemic conditions, some modifications occur in the amino acids located on the N-terminus of the human albumin molecule. Ischemia-modified albumin (IMA) is a marker formed after damage in the N-terminal region of albumin. The altered N-terminus can no longer bind transition metals, such as cobalt. The causes of the increases in IMA have been shown to be endothelial or extracellular hypoxia, acidosis, and free oxygen radicals. IMA, an early marker of ischemic disorders, is also a candidate marker for the detection of ACS. An assay measuring IMA might represent a promising marker for the identification of patients with myocardial ischemia. The aim of this study was to evaluate the clinical utility of IMA in the assessment of ACS as well as other medical disorders in light of the recent literature.

Keywords: acute coronary syndrome; biochemistry; ischemia-modified albumin.

Introduction

Every year, approximately 6 million people are admitted to hospitals with chest pain. Only 17% of these are eventually diagnosed with acute coronary syndrome (ACS) [1]. ACS is a constellation of signs and symptoms resulting from an imbalance between myocardial oxygen supply and demand [2]. In the emergency department (ED), evaluation of patients with chest pain is difficult and challenging [3]. Although cardiac biomarkers like myoglobin, creatine kinase MB (CK-MB) fraction, and the troponins (Tn) are sensitive for the identification of patients with myocardial necrosis, their ability to identify patients with ACS remains limited [4]. There are still unnecessary admissions to expensive coronary care units, step-down units, and non-intensive care beds. Further, of those patients with myocardial infarction (MI), 1%–2% are sent home [5]. Mortality rates of missed diagnoses in patients sent home are twofold greater than those of patients admitted. Thus, identification of myocardial ischemia during the early, reversible stage of ACS is a center of interest for researchers [6]. In the setting of myocardial ischemia, some modifications occur in the amino acids located on the N-terminus of the human albumin molecule. The altered N-terminus can no longer bind transition metals, such as cobalt. An assay measuring IMA might represent a promising marker for the identification of patients with myocardial ischemia [4]. In this review, our purpose was to evaluate the clinical utility of IMA in the management of ACS as well as other medical disorders in light of the recent literature.

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Structure of IMA

Human serum albumin (HSA) is the most abundant multifunctional protein in the blood, with a mean concentration of 0.63 mmol/L. It consists of 585 amino acid residues (66.5 kDa) folded into three homologous domains as determined by X-ray crystallography, is synthesized in the liver, and has a half-life of 19 days [7]. Extensive studies of the metal-binding properties of HSA have revealed that metal ions bind to a wide variety of sites [3]. The best characterized metal binding site is located at the N-terminus, which comprised the amino acid sequence N-Asp-Ala-His-Lys. Of these four residues, the first three have been shown to be essential for metal binding, while the fourth one, lysine,

is not essential. These sites have particularly high affinity for copper and nickel. The groups that participate in this binding have been shown to be the α-amino group, the two intervening peptide nitrogen atoms, the δ-imidazole nitrogen from His3 and the side-chain carboxyl group of Asp1 [8]. In the presence of ischemia, structural changes take place in the N-terminus of albumin that rapidly reduce its binding capacity for transition metal ions, Co^{2+} and Ni^{2+} [9, 10]. IMA is a marker formed after damage in the N-terminal region of albumin. The causes of the increases in IMA have been shown to be endothelial or extracellular hypoxia, acidosis, and free oxygen radicals [11].

Analysis of IMA

The analytical methods of IMA assay are based on the ability of protein to chelate the cobalt cation. In proteins, several sites that have the ability to bind divalent metals exist. The most interest to date has been focused on the binding of the N-terminal region of the protein with transition metals, for example, cobalt [12]. The mechanism whereby IMA represents a marker of ischemia is based upon the fact that HSA has the ability to bind certain transition metal ions, particularly cobalt and copper, at the N-terminus [13]. Albumin in which the N-terminus is either damaged or occupied by copper is termed as IMA, and the test is referred to as the ACB test [3]. The ACB test is a quantitative assay that measures IMA in human serum. In principle, in the serum of patients with ischemia, cobalt added to the serum does not bind to the N-terminus of IMA. Thus, it leaves more free cobalt to react with dithiothreitol and form a darker color [14]. Human serum is collected in serum separator tubes and may be incubated with a fixed amount of cobalt in the form of cobalt chloride. Then, dithiothreitol is added to react with the cobalt not bound to the N-terminus to form a measurable color. The absorbance is measured by spectrophotometer [9]. Blood samples need to be analyzed rapidly to avoid sample dilutions. Samples may be frozen at below –20 °C or lower for an indefinite period [15]. This assay is reported to be positive within 6–10 min of ischemia and remains so up to 6 h later, allowing detection before the development of myocardial necrosis [16, 17]. IMA measurement is influenced by some analytical matrices, especially the presence of serum albumin concentrations outside the reference interval. Serum albumin concentration may show great variance among individuals; therefore, serum albumin concentration should be included in the interpretation of IMA results [12]. It was also reported that albumin-adjusted IMA (Adj-IMA) was better correlated than IMA when the patients have low levels of serum albumin. The formula suggested by Lippi et al. has been used for calculation of Adj-IMA levels expressed as individual serum albumin concentration/median albumin concentration of the population×IMA value [18].

Use of IMA in ACS

Evaluation of patients who present to the hospital with a complaint of chest pain or other signs or symptoms of ACS is time-consuming, expensive, and problematic [5]. ACS represents a continuum of disease ranging from unstable angina, associated with reversible myocardial cell injury, to ST-segment elevation myocardial infarction (STEMI), associated with irreversible myocardial necrosis. The detection of ischemia prior to infarction represents a diagnostic and therapeutic challenge. Theoretically, if ischemia can be detected prior to progression to necrosis, it may be possible to intervene earlier than at present to either limit or prevent myocardial damage [12]. Currently, cardiac troponin (cTn), a marker of myocardial cell necrosis, is the biomarker defined by the European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA) as the standard for detection of myocardial injury. Further, in the clinical setting of ischemia, an increased cTn is the basis of the diagnosis of MI. However, since it may take 2 to 6 h before cTn becomes increased above a predetermined reference limit in the circulation, the quest continues to identify an early, and ideally, a cardiac tissue-specific marker of myocardial ischemia.

The observation that serum albumin in patients with myocardial ischemia produced a lower metal binding capacity for cobalt than serum albumin in non-ischemic normal controls led to the development of the recently Food and Drug Administration (FDA)-cleared ACB test [6], which is the first FDA-cleared assay to attempt to detect myocardial ischemia [14, 19, 20].

Sinha et al. [13] revealed that the sensitivity of IMA for the diagnosis of acute ischemic chest pain is significantly greater than that of electrocardiography (ECG) and cardiac troponin T (cTnT), used alone or combined. In 2004, with 208 patients who presented to the ED with chest pain, they evaluated IMA in conjunction with ECG and cTn. They reported that 65% of the positive ACS diagnoses were unstable angina patients with normal cTnT. ECG identified 32% on admission; however, IMA identified 91%. They also reported that IMA had high sensitivity for prediction of a discharge diagnosis of ACS, but it had comparatively low

specificity in contrast with presentation Tn, which has high specificity but very low sensitivity. In this study, although two patients with angiographically normal coronary arteries presented positive IMA results, researchers associated these results to dynamic vasoconstriction and coronary artery spasm. This study was one of the earliest studies to show that the sensitivity of IMA for the diagnosis of acute ischemic chest pain was significantly greater than that of ECG and cTnT [13]. Roy et al. [21] studied 131 patients who presented to the ED with symptoms suggestive of ACS but with normal or non-diagnostic ECGs. With a cutoff value of 85 U/mL, IMA had a high sensitivity (90.6%). When combined with TnT, the sensitivity increased to 92.2%. They reported that after multivariate analysis, independent predictors of ACS were found to be IMA levels >85 U/mL, age, and prior myocardial ischemia. Liyan et al. [22] reported in their study that IMA value was significantly higher in patients with ACS compared with non-ischemic chest pain. Their study also showed that the combination of heart-type fatty acid-binding protein (H-FABP) and IMA is an independent sensitive method for the identification of ACS in patients presenting to the ED with acute chest pain and negative cTnT. However, because the study was carried out with a small number of patients (the number of patients with acute MI was 43), the threshold value for IMA used in their study needed to be confirmed. Chawla et al. [23] compared CK-MB and IMA in patients with chest pain. The study included a small group of patients (n=25). They found that IMA was significantly raised in ischemia patients compared to controls as well as compared to patients who did not have cardiac ischemia. For the detection of ischemia, sensitivity and specificity of IMA were found to be superior according to the CK-MB assay.

They also proposed IMA as a marker to identify non-cardiac chest pain cases, as it has a very high negative predictive value (85%). In another study, Aggarwal et al. [3] reported that IMA levels were significantly elevated in patients with chest pain with myocardial ischemia as compared to control groups. A significant positive correlation was observed between IMA levels and CK-MB levels and between IMA levels and Tn-I levels. However, they concluded that the IMA assay is a sensitive but not very specific marker for the early detection of myocardial ischemia. They suggested combining IMA with other biomarkers to increase specificity [3]. Anwaruddin et al. [4] also demonstrated that by using a diagnostic cutoff point of 90 U/mL, the assay for the measurement of IMA was sensitive for the diagnosis of myocardial ischemia at the time of clinical diagnosis and had a high negative predictive value.

They also found that the combination of the triple screen (myoglobin, CK-MB, and Tn-I) plus IMA resulted in superior sensitivity for the detection of ACS, with a simultaneous increase in the negative predictive value to 92% [4]. Bali et al. [9] demonstrated that the independent prognostic value of IMA was greater than that of conventional markers such as Tn-I and C-reactive protein for non-ST-segment elevation (NSTE) ACS patients. The small sample size was mentioned as being a limitation of the study (n=79). In their conclusion, baseline IMA level was associated with both short- and long-term recurrent ischemic events in patients admitted to the hospital for NSTE ACS. In addition, a cutoff of 109 U/mL had a good negative predictive value and could be used in daily clinical practice [9]. Behera et al. [24] aimed to evaluate the diagnostic efficacy of IMA and its correlation with lipid profile and oxidative stress in acute MI patients admitted to the ED. In their study, the presentation of ECG combined with cTnT identified 71% of the patients. With the addition of IMA to ECG or cTnT, or both, diagnostic sensitivity increased. It was reported that the ability of IMA to detect ischemia before myocyte destruction would allow for earlier and more accurate management decisions.

In a multicenter study, with a cutoff value of 85 U/mL and a negative predictive value of 81%, IMA was found to be inadequate to detect or exclude ACS [25]. Charpentier et al. [26] reported their comparison of IMA and H-FABP in patients with ACS. The receiver operating characteristics curve in their study did not show a cutoff value to discriminate patients according to the presence of ACS. They concluded that neither IMA nor H-FABP was able to exclude ACS on admission in patients with chest pain. They also reported that while IMA was not predictive of the ACS diagnosis (odds ratio=1.23, 95% confidence interval [CI]=0.87 to 1.81), H-FABP was predictive of the ACS diagnosis.

In the French Nationwide OPERA study, IMA levels of patients were measured within 24 h, and patients' follow-up data were recorded after 1 year. It was reported that IMA measured within 24 h could be a strong and independent predictor of cardiac outcome and might be helpful to identify those requiring more aggressive medical management [27].

Maneewong et al. [28] reported that serum IMA and protein carbonyl (PC) levels significantly increased in non-STEMI (NSTEMI) according to healthy controls. Their study showed that the diagnosis of NSTEMI was not improved by the combination of serum IMA and PC levels.

These two biomarkers revealed poor sensitivity. They found that the sensitivity and negative predictive value (51.52% and 64.44%, respectively) of IMA were low. Their findings demonstrated that IMA was not a good diagnostic marker for NSTEMI. However, Ozdem et al. [29]

reported that IMA could be used as an early biomarker in ACS. They determined a cutoff value of 74.1 U/mL and found that sensitivity and specificity of IMA were 60.98% and 89.29%, respectively. Further, they reported that the different cutoff values found in various studies were probably associated with different levels of ischemia and different methods of IMA measurement. In 2008, Talwalkar et al. [30] measured serum levels of IMA in 89 sequential patients who presented to the emergency room with chest pain, for which serum TnT was ordered. They reported that although IMA is a sensitive marker for ischemia, its sensitivity decreases especially in conditions associated with transient/reversible ischemia. In their conclusion, they found that serum IMA was a useful marker for the diagnosis of ACS. They determined a significant relationship between TnT and IMA. The combination of the high sensitivity of TnT and high negative predictive value of IMA makes them independent predictors of developing ACS. Despite the fact that IMA is a useful marker for ischemia, Koc et al. [31] revealed that IMA could not adequately reflect stress-induced ischemic changes on myocardial perfusion scintigraphy. Peacock et al. [32] investigated literature data to determine the availability of IMA in ACS risk stratification. Eight studies of more than 1800 patients were included in the meta-analysis. The TnT sensitivity and negative predictive value for acute ACS were 94.4% and 97.1%, respectively, and for longer-term outcomes, were 89.2% and 94.5%, respectively. A negative triple prediction test of a nondiagnostic ECG, negative Tn, and negative IMA was found to have high negative predictive value for excluding ACS in the ED [31]. Van Belle et al. [27] reported that in patients with acute MI, measurement of IMA within 24 h is a strong and independent predictor of cardiac outcome at 1 year and may help identify those requiring more aggressive medical management. Recently, Toker et al. [33] compared serum and saliva levels of IMA in patients with acute MI. They found that serum IMA levels were significantly higher in the first and second days, while salivary IMA levels were significantly higher in the first day in MI patients compared to controls. This seems to be a promising finding for further investigations. Such a method may help reduce mortality and morbidity through its availability and simplicity. It also has advantages both in time and cost. Studies on usefulness of IMA in ACS are summarized in Table 1.

Table 1: Summary of studies on utility of ischemia-modified albumin in ACS.

Study (number of patients) [reference number]	Useful	Moderate	Useless
Roy et al. (n=131) [21]	×		
Liyan et al. (n=108) [22]	×		
Chawla et al. (n=25) [23]	×		
Aggarwal et al. (n=100) [3]	×		
Anwaruddin et al. (n=200) [4]	×		
Bali et al. (n=79) [9]	×		
Behera et al. (n=35) [24]	×		
Bhardwaj et al. (n=318) [25]			×
Charpentier et al. (n=677) [26]			×
OPERA Study (n=471) [27]	×		
Maneewong et al. (n=33) [28]		×	
Ozdem et al. (n=196) [29]	×		
Talwalkar et al. (n=89) [30]	×		
Koc et al. (n=56) [31]		×	
Peacock et al. (review) [32]	×		
Toker et al. (n=60) [33]	×		
Sinha et al. (n=208) [13]	×		

IMA in other ischemic conditions

An increasing number of studies have shown that IMA levels rise in a number of acute ischemic conditions such as cerebral infarct, MI, pulmonary infarct, and mesenteric infarct [34]. Turedi et al. [35] conducted many studies investigating the usefulness of IMA measurement in various diseases. In one of their studies, they found that IMA levels increased in patients with pulmonary embolism (PE) when compared to healthy subjects. In another study, they compared IMA and D-dimer in the diagnosis of PE. Even though IMA was not found to be superior to D-dimer in the diagnosis of PE, it was reported that IMA could be an alternative marker. It was also underlined that IMA was much more cost-effective [36].

Turedi et al. [37] also investigated the diagnostic role of IMA in carbon monoxide (CO) poisoning. Serum IMA levels of the patients with CO poisoning were higher than those of the control group even on admission and at the third hour of the treatment. However, serum IMA levels were not correlated with the measured carboxyhemoglobin (COHb) levels and the only certain result of this study was that IMA levels increased in CO-poisoned patients. Mentese et al. [34] investigated the usefulness of IMA level in the diagnosis of deep venous thrombosis (DVT). They made a definite diagnosis of DVT with Doppler ultrasound. They determined that DVT was associated with raised serum IMA levels, but IMA levels were not suitable as a diagnostic marker for DVT.

In an experimental study, it was demonstrated that serum IMA levels rose in the acute period of an experimental mesenteric ischemia model in rats. It was concluded that IMA could be useful in the early diagnosis

of acute mesenteric ischemia [38]. Abboud et al. [39] studied 118 consecutive patients presenting within 3 h of the onset of cerebrovascular disease (CVD). Serum IMA levels of patients with brain ischemia increased within 24 h. In another study, a statistically significant difference between the mean IMA levels in brain ischemia, intracranial hemorrhage, and subarachnoid hemorrhage patients and the mean control patient IMA levels was determined. Thus, it was reported that serum IMA levels are increased in patients with CVD [40]. In end-stage renal disease (ESRD) patients, due to the generalized hypoxic effect of anemia, serum IMA levels were found to be high [41]. In another study, the IMA levels of ESRD patients, both pre- and post-hemodialysis, were significantly higher than those of the control group [42]. It was also reported in another study that serum IMA levels predicted mortality in ESRD patients. This conclusion is probably due to the negative effects of renal disease on the heart. ESRD patients with elevated IMA levels had larger left ventricle (LV) size, decreased systolic function, and greater estimated LV filling pressures [43]. When skeletal muscle injury occurs, the IMA level increases. Thus, when IMA is used to detect myocardial ischemia, skeletal muscle ischemia must be excluded [44]. Similarly, Lippi et al. [45] reported that the concentrations of both CK-MB and IMA were significantly increased in athletes subjected to high workload endurance training, whereas the concentrations of cTnT and myoglobin were not influenced by physical exercise in the mid-term. However, a forearm ischemia model revealed a decrease in serum IMA levels, while lactate and ammonia levels increased [17]. In another study, it was also reported that IMA was significantly lower immediately after exercise-induced leg ischemia in patients with DVT and was related to disease severity [46]. Crimean-Congo hemorrhagic fever (CCHF) is a lethal disease caused by a virus of the Bunyaviridae family. The viral infection occurs due to tick bite or through the blood or body fluids of domestic animals or CCHF patients. Mentese et al. [47] investigated the IMA levels in patients with CCHF. They found that IMA levels were significantly higher in patients with CCHF. In addition, they found that IMA levels were higher in patients with hemorrhage when compared to patients without hemorrhage. A similar relationship was revealed by Zuwała-Jagiełło et al. between IMA and inflammation in chronic hepatitis C patients with diabetes [48].

IMA has also been studied in other diseases. Piwowar et al. [49] reported that IMA levels in patients with diabetes mellitus were significantly higher than controls. In another report, it was revealed that patients with hypertension had elevated IMA levels [50]. Also, it was reported that obesity caused increase in IMA levels indicating risk of ischemia in obese people [51]. In a study, higher levels of IMA were determined in patients who experience seizure, and it was reported that it could be used for differentiation of seizures [52]. Measurement of IMA in cord blood samples of newborns of preeclamptic mothers may reveal ischemia and oxidative stress [53]. Even though it was found that IMA levels are not affected in DVT, it may be a useful marker for diagnosis of PE [35, 54]. The role of IMA in cancer has also been studied; however, its usefulness in cancer still needs to be clarified [55–57].

Conclusions

An increasing number of studies have shown that IMA levels increase in a number of acute ischemic conditions such as cerebral infarct, myocardial infarct, pulmonary infarct, CO poisoning, anemia, and mesenteric infarct, suggesting that IMA may be useful as a diagnostic marker. Although there are many studies investigating the role of IMA in the assessment of ACS, many questions about the usefulness of IMA remain unanswered. The main limitation of IMA in the evaluation of ACS is its low specificity. However, it may be a useful test to rule out ACS in clinical conditions with negative cTn and a negative ECG. According to the current literature, it can be concluded that a more sensitive and specific marker for earlier and more definite diagnosis of ACS is needed.

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