Biomarkers, 2010; 15(8): 655–662

informa
healthcare

REVIEW ARTICLE

Current role of ischemia-modified albumin in routine clinical practice

Alberto Dominguez-Rodriguez[1], and Pedro Abreu-Gonzalez[2]

[1]*Hospital Universitario de Canarias, Department of Cardiology, Tenerife, Spain, and*[2]*University of La Laguna, Department of Physiology, Tenerife, Spain*

Abstract

Background: Ischemia-modified albumin has been proposed as a useful rule-out marker for the diagnosis of acute coronary syndrome in the emergency department.

Objective: To perform a review of ischemia-modified albumin use in the clinical practice.

Methods: We performed a comprehensive literature search by using electronic bibliographic databases.

Conclusion: Although the main limitation of ischemia-modified albumin at present is its low specificity, it may be a useful test to rule out acute coronary syndrome from low to moderate pre-test probability conditions with negative cardiac troponins and a negative ECG.

Keywords: *Acute coronary syndrome; chest pain; acute myocardial ischemia; Emergency department*

Introduction

The triage and treatment of patients who present to emergency departments (EDs) with symptoms potentially indicative of acute cardiac ischemia remain problematic and continue to challenge clinicians. More than 6 million patients present annually to US EDs with suspected acute coronary syndromes (ACS) of whom only 17% are finally diagnosed with coronary artery disease. Patients are hospitalised or held for observation and, although ACS is often ruled out, this imposes a substantial financial burden and inconvenience to the patient and medical system (Duseja&Feldman 2004, Roy et al. 2004, Peacock et al. 2006).

Failure to recognise ACS has unfavourable consequences not only for patients, but for physicians too. Missed acute cardiac ischemia continues to be one of the major causes of malpractice litigation against emergency physicians. Twenty percent of ED-related malpractice compensation is expended on patients with complications because of myocardial ischemia (Duseja&Feldman 2004). Non-hospitalised patients with acute myocardial infarction (AMI) have a three times higher risk of death than those who are hospitalised. Missed AMIs result for several reasons, including atypical presentation, or the initial insensitivity of the current tools,i.e. electrocardiogram (ECG) and biomarkers (Pope et al. 2000).

The diagnostic approach to ACS remains one of the most difficult and controversial medical challenges. Traditionally, the diagnosis of acute cardiac ischemia relies on the combination of chest pain, ECG changes and serum marker elevation. Clinical symptoms and characteristic ECG alterations have been useful tools in the diagnosis of AMI (Rajappa & Sharma 2005). However, symptoms may be non-specific in up to one-third of chest pain patients, and the ECG misses up to 50% of the patients who have had an AMI (Ryan et al. 1996, Christenson & Azzazy 1998, Storrow & Gibler 2000). Hence, the diagnosis of ACS has become increasingly dependent on serum markers of myocardial injury (Lippi et al. 2006a). Although troponins have greater sensitivity, they are unsuitable for early diagnosis, as nearly 50% of patients may present at the ED with non-diagnostic concentrations. This happens either because patients present early after the onset of AMI and troponin levels are not

Address for Correspondence: Alberto Dominguez-Rodriguez, Hospital Universitario de Canarias, Department of Cardiology,Ofra s/n La Cuesta E-38320,Tenerife, Spain.Tel: + 34 922 679040. Fax: + 34 922 362716. E-mail: adrvdg@hotmail.com

(Received 28 June 2010; revised 01 August 2010; accepted 02 August 2010)

ISSN 1354-750X print/ISSN 1366-5804 online © 2010 Informa UK, Ltd.
DOI: 10.3109/1354750X.2010.513449

yet detectable or patients present with acute myocardial ischemia without necrosis (Morrow et al. 2003).

Patients with myocardial ischemia pose a greater challenge than patients with AMI because the patient may have acute chest pain, a non-diagnostic ECG and normal levels of troponins. Thus, despite the fact that patients with myocardial ischemia are at high risk for subsequent coronary events, they are often discharged because there is not enough evidence to justify hospital admission (Lippi et al. 2006b). Hence, the usefulness of the standard biomarkers of myocardial necrosis for the early and confident exclusion of the diagnosis of myocardial ischemia is limited. New markers capable of identifying early myocardial ischemia before it progresses to the irreparable myocardial cell damage might play an important role in the clinical setting because they will give the emergency physician the opportunity to intervene and prevent progression to infarction (Figure 1) (Anwaruddin et al. 2005, Lippi et al 2006a).

The ideal biochemical marker of myocardial ischemia should be released solely from the myocardium and should achieve high concentrations and rapid release into the blood stream at the time of ischemia. Furthermore, its concentrations should be related to the extent of injury and should be detectable in the blood for long enough to be measured even in late-presenting patients. Another feature of the ideal biomarker is a steep decrease after a period of 24 h, so that recurrent ischemia can be easily detected. Optimally, detection of the biomarker should be simple to perform with a turnaround time of 30–60 min or less and it should have a reliable analytic performance at a reasonable cost (Morrow et al. 2003).

We performed a comprehensive literature search using electronic bibliographic databases (MEDLINE, EMBASE and the Cochrane Library) and combinations of the following keywords: ischemia modified albumin AND acute coronary syndrome OR acute myocardial infarction OR emergency department. Bibliographies of all selected articles and reviews were searched for other relevant articles.

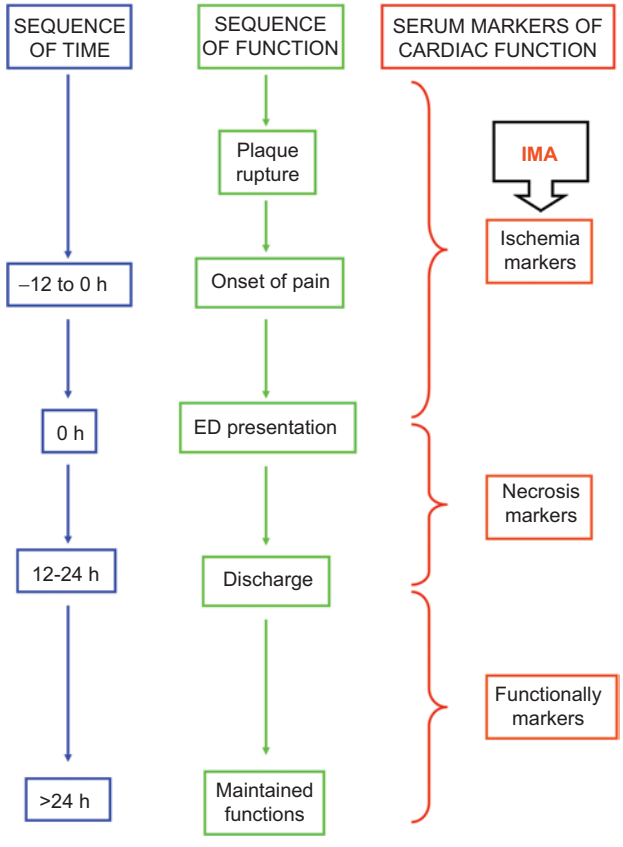

Figure 1. Temporal sequencing and functional in acute coronary syndrome: ischemia-modified albumin (IMA) as an early ischemia marker.ED, Emergency department.

Ischemia-modified albumin

ACS represents 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 an atheromatous plaque (Libby 2001, Toutouzas & Stefanadis 2006). The consequences of plaque rupture and subsequent vascular occlusion can be divided into three phases. There will be an initial phase of myocardial ischemia. If it is prolonged, this will then result in cardiac necrosis. Finally, there will be a phase of repair and vascular remodelling.

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 (Collinson & Gaze 2007). Currently, three markers have been proposed: choline, free fatty acids and ischemia-modified albumin (IMA) (Apple et al. 2005). Of these, only IMA is currently available as a licensed test for routine clinical application, measured using the Albumin Cobalt Binding (ACB®) assay (Bar-Or et al. 2000).

The postulated mechanisms of IMA generation include: (1) reduced blood flow due to ruptured atherosclerotic plaques results in insufficient oxygen to tissue and causes a lower pH; (2) copper II is released from weak binding sites on plasma proteins and metal bound at the N-terminus; (3) in the presence of ascorbic acid (AA), copper II is converted to copper I and this reacts with oxygen to form superoxide radicals ($O_2^{\cdot -}$); (4) the enzyme superoxide dismutase (SOD) dismutates the superoxide radicals, forming hydrogen

peroxide (H_2O_2); this is harmlessly degraded into water and oxygen by the action of a second enzyme, catalase; (5) in the presence of metals such as copper or iron, hydrogen peroxide undergoes a Fenton reaction, forming hydroxyl free radicals (OH°); (6) the copper II is scavenged by human serum albumin, on which it binds tightly to the N-terminus; (7) hydroxyl free radicals are highly reactive and capable of damaging nucleic acids, lipids and proteins, including albumin; one site of damage is the N-terminus, where hydroxyl free radical alters amino acids; (8) altered albumin is incapable of binding to copper II; and (9) bound copper is released from the albumin, where it may be taken up again by the N-terminus of another albumin in a chain reaction so that the process of albumin binding and hydroxyl free radicals formation is repeated (Figure 2) (Gaze 2009).

There is little doubt, if any, that IMA levels increase during myocardial ischemia triggered by a primary reduction of blood flow, as seen in patients during percutaneous coronary intervention. Several studies have shown a good correlation among objective markers of myocardial ischemia, such as lactate levels (Sinha et al. 2006), isoprostane concentrations (Sinha et al. 2003) and IMA levels, in this setting. The production of reactive oxygen species during balloon occlusion and reperfusion in patients undergoing percutaneous coronary intervention (Iuliano et al. 2001) and in the ACS setting (Sinha et al. 2004), where intracoronary thrombosis causes serious reductions in coronary blood flow, may result in the chemical modification of albumin that leads to IMA production. A recent study, by our group, correlating IMA with levels of melatonin in ST-segment elevation myocardial infarction patients, supports the suspicion that reactive oxygen species may be responsible for the creation of IMA (Dominguez-Rodriguez et al. 2008b). Moreover, the combination of ischemia–reperfusion causes numerous and complex reactions in tissues which culminates in the mutilation of essential molecules and organelles in a number of cells including components of the coronary endothelium and myocardium with the recruitment of circulating blood elements, e.g. leukocytes and platelets (Iuliano et al 2001). During the transient ischemia and the period of reperfusion many cells generate derivative products of oxygen that are toxic to the heart. Indeed, the partially reduced oxygen metabolites, referred to as reactive oxygen species, are accepted as accounting for much of the cardiac damage that occurs during ischemia–reperfusion injury in patients with ST-segment elevation myocardial infarction(Iuliano et al 2001). *In vivo*, modifications of the albumin N-terminus are proposed to be related to the reactive oxygen species production during myocardial ischemia–reperfusion (Sinha et al 2006). *In vivo* generation of IMA might be interpreted as an efficient endogenous mechanism of response to ischemia, preventing myocardial damage or limiting the extent of myocytenecrosis (Lippi et al 2006a).

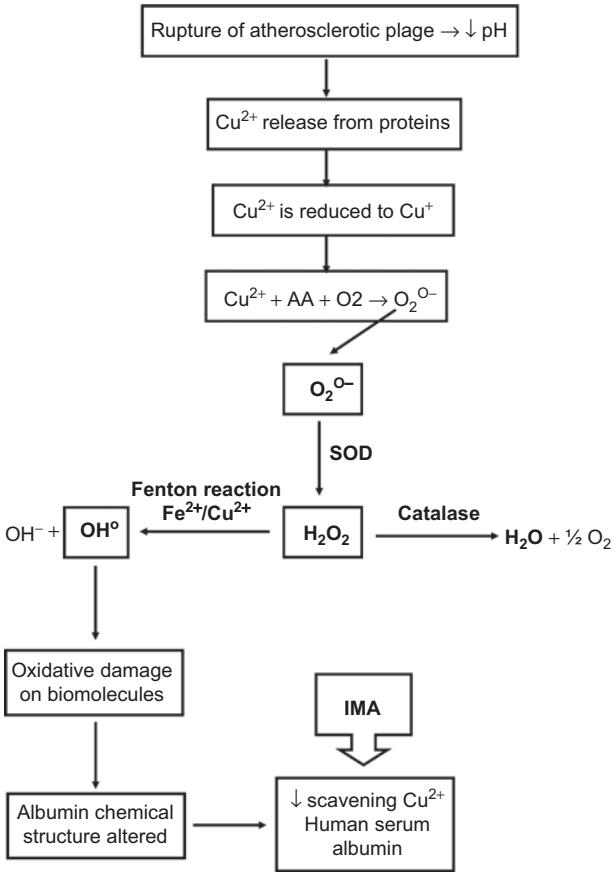

Figure 2. Scheme of ischemia-modified albumin (IMA) generation with direct involvement of free radicals in acute coronary syndrome. AA, ascorbic acid; SOD,superoxide dismutase.

Measuring IMA

The analytical methods of IMA assay are based on the ability of protein to chelate the cobalt cation. In proteins, several sites exist that have the ability to bind divalent metals. The most interest to date has been focused on the bindingof the N-terminal region of the protein with transition metals, for example cobalt (Bhagavant et al. 2003). Bar-Or et al. (2000), found that serum albumin of patients with myocardial ischemia exhibited lower metal-binding capacity for cobalt than serum albumin of normal subjects. The principle of this test measures the cobalt capacity to bind to albumin in a serum sample. A cobalt chloride solution is added to serum and, after incubation, cobalt not bound to the N-terminus of the albumin is detected using dithiothreitol as a developer of colour in a spectrum ranging between 470 and 500 nm.

An inverse relationship exists between the amount of albumin-bound cobalt and the intensity of the colour formation. In serum of normal subjects, the added cobalt binds to the N-terminus of the albumin, leaving a small amount of free cobalt that reacts with dithiothreitol producing a low-intensity chromogen colour. In contrast, in the serum of ischemic patients, less cobalt binds to the N-terminus of albumin, leaving more free cobalt to react with dithiothreitol to produce a high intensity in the chromogen colour.

The manual assay for detecting IMA, developed by Bar-Or et al. (2000), has been adapted to run on the Roche Cobas Mira® Plus and CobasFara® automated clinical chemistry platform and designated as ACB® (Fagan et al. 2002). Although technically both tests have the same chemical principle, some differences exist in the expression of results that make it difficult to compare the results obtained by different research groups. The ACB® assay gives IMA values with arbitrary units (kU l^{-1}) instead of absorbance units (A.U.) as in the manual assay. The optimum IMA cut-off value for ruling out ACS also differs from study to study (Pantazopoulos et al. 2009). At this time, the main problem is the absence of calibrators based on the mass concentration of IMA. Standardization of the ACB® assay by a human albumin universal calibrator could improve that assay performance and transference of results (Hakligor et al. 2010).

There is evidence that IMA measurement is influenced by some analytical matrix, especially the presence of serum albumin concentrations outside the reference interval (Gaze et al. 2006). Serum albumin concentration may show great variance among individuals, therefore serum albumin concentration should be included in the interpretation of IMA results (Lee et al. 2007). The adoption of a corrective formula, which takes into account the concentration of protein in the sample, could have an effect on this interference, allowing the generalization of this parameter in any population (Lippi et al. 2007). Therefore, Jalan et al. (2009), use the term IMAR (ischemia-modified albumin, expressed as an albumin ratio) in individuals with advance cirrhosis with damage to the circulating albumin. In their study, IMAR was better correlated than IMA with the severity of cirrhosis and it may have a prognostic role in acute-on-chronic liver failure. Other serum parameters such as haemoglobin and triglycerides had no any effect on the IMA assay (Gidenne et al. 2004). With respect to the conditions of the IMA samples, they should be stored prior to analysis. It may be critical in influencing the results. Therefore, each laboratory should establish a time period and temperatures (range –20 to –70ºC) of storage of samples for reliable results (Beetham et al. 2006).

The biological variation of IMA has been studied. Gender differences in IMA among healthy individuals do not occur but IMA levels are statistically different between Caucasian and Black populations (Govender et al. 2008). Moreover, there have been reports of elevated IMA under other conditions where cardiac ischemia and troponin elevation may also occur, including acute stroke, pulmonary embolus, polytrauma, end-stage renal disease, and vascular and non-vascular surgery (Gaze 2009). Likewise, data exist suggesting that the presence of co-existing lactic acidosis might affect assay performance (Zapico-Muñiz et al. 2004, Hakligor et al. 2010).

Various studies have shown that IMA increases within minutes after the onset of ischemia, remains elevated for 6–12 h, and returns to normal within 24 h (Pantazopoulos et al. 2009). Thus, it may be a valuable aid for the clinician because it enables early detection of ischemia before the development of myocardial ischemia.

Clinical applications of IMA in cardiac ischemia

Most patients brought to the hospital with chest pain and suspected of ACS are eventually ruled out for AMI and active unstable coronary disease. The ideal role of an ischemia marker would thus be as a rule-out test. The most logical place to use such a test is in the ED (Gaze 2009). Table 1 shows test characteristics of IMA in combination with traditional diagnostic markers of ACS.

Christenson et al. (2001) demonstrated that the ACB® assay has a high negative predictive value and sensitivity at the time of presentation at the ED for predicting troponin-negative or -positive results 6–24 h later. A study on ED presentations examined 208 patients and the diagnostic sensitivity of IMA measurement alone was 82% at 46% specificity in samples taken within the first 3 h. A combination of ECG, cardiac troponin T and IMA showed 95% sensitivity for diagnosis of ACS at presentation (Sinha et al. 2004). A study involving patients with symptoms suggestive ofACS but with normal or non-diagnostic ECGs who came to the ED within 3 h of chest pain documented outcomes at 30 days of ACS (unstable angina or myocardial infarction with non-ST-segment elevation) or non-ischemic chest pain. They measured IMA at presentation and reported positive (odds ratio (OR) 2.96, 95% confidence interval (CI) 1.91–4.56) and negative (OR 0.33, 95% CI 0.21–0.52) OR using a threshold of 93.5 U ml^{-1} (Roy et al. 2004a). In a subsequent study on 538 patients admitted for chest pain evaluation, admission measurement of IMA, plus cardiac troponin T indicated 100% sensitivity for prediction of a final diagnosis of AMI (Collinson et al. 2006). The presence of elevated IMA and elevated cardiac troponin T on admission predicted 21% risk of major adverse cardiac events compared with patients for whomneither were elevated, even in patients where the final diagnosis excluded AMI by troponin-based criteria.

Table 1. Test characteristics of ischemia-modified albumin(IMA) in combination with traditional diagnostic markers of acute coronary syndrome (ACS).

First author (year)	Sample size	Combination of test	Sensitivity (%)	Specificity (%)	Composite ischemic end point
Christenson et al., 2001	224	IMA, cTnI	83	69	ACS
Sinha et al., 2004	208	IMA, cTnT, ECG	95	42	ACS
Roy et al., 2004a	131	IMA, cTnT	75	75	ACS
Collinson et al., 2006	538	IMA, cTnT	100	34.5	AMI
Keating et al., 2006	399	IMA, cTnI	97.6	13.6	Ischemic cardiac chest pain
Worster et al., 2005	189	IMA	92.3	24.3	Serious cardiac events
Hjortshøjet al., 2010	107	IMA	86	49	ACS
Aparci et al., 2007	50	IMA	70	82	Mortality
Peacock et al., 2006	1800	IMA, cTn, ECG	94	-	ACS

AMI, acute myocardial infarction; ECG, electrocardiogram; cTn, cardiac troponin; cTnT, cardiac troponin T; cTnI, cardiac troponin I.

Not all investigators consider the diagnostic performance of IMA either alone or in combination with cardiac troponin, or other biomarkers of necrosis, to be adequate. A prospective observational study assessing low-risk patients with chest pain showed that the measurement of IMA and cardiac troponin I at presentation had a high sensitivity rate (97.6%) but markedly lower specificity rates (13.6%) (Keating et al. 2006).Another large prospective study on 189 patients presenting at the ED with chest pain indicated elevated IMA to be a poor predictor of cardiac events within the next 72 h (Worster et al. 2005). Likewise, Hjortshøj et al. (2010) enrolled 107 subjects admitted with suspected ACS;the sensitivity of admission IMA for a final diagnosis of ACS was 86%, specificity 49% and a negative predictive value 88%. Recently, a large prospectivestudy on 248 patients presenting at the ED with symptoms suggestive of ACS, did not support the use of IMA as a negative predictor for ACS. All patients had positive IMA results using the 85 Uml^{-1} cut-off value recommended by the manufacturer. Receiver-operating characteristic curves failed to show improved cut-off points for diagnosis with raised 12 h troponin levels or ACS; the area under the curve was 0.52 and 0.53, respectively (Ming-Hui Lin et al. 2010).

Conversely, in a study by Aparci et al. (2007), 50 ACS patients were followed for 1 year after the ischemic event. In patients with IMA values above 477 Uml^{-1}, mortality was significantly higher than in those with values below 477 Uml^{-1}. The sensitivity and specificity for 1-year mortality at the cut-off point of 477 Uml^{-1}were 70% and 82%, respectively. The most consistent finding in all the studies of IMA was a high negative predictive value. This has been highlighted in a meta-analysis of more than 1800 patients which concluded that, in a large ED cohort with suspected myocardial ischemia, the combination of ECG, troponin and IMA has 94.4% sensitivity and 97.1% negative predictive value for the final diagnosis (Peacock et al. 2006). Nevertheless, several issues have slowed the progress of IMA as a standard marker in the ED. First, the general concept of a marker of ischemia and its possible flaws has been regarded with suspicion within the cardiology community. Second, complicated issues regarding handling and storage of samples have limited widespread use in automated laboratories and clinical trials (Hjortshøj et al. 2010).

IMA has been investigated in different study populations. Research from our group has shown that IMA is related significantly to left ventricular ejection fraction and represents an early marker of left ventricular dysfunction in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention (Dominguez-Rodriguez et al. 2008a). Studies have also shown that IMA may be a useful biomarker for the identification of incomplete ST-segment resolution in patients with ST-segment elevation myocardial infarction presenting to hospital within 6 h of the onset of pain (Dominguez-Rodriguez et al. 2009b). Likewise, we have demonstrated that IMA level obtained at admission is a powerful indicator of short-term mortality in patients with AMI, but it does not seem to be a marker that adds prognostic information to the validated Thrombolysis in Myocardial Infarction risk score (Dominguez-Rodriguez et al. 2009a). Recently, Ven Bell et al. (2010) have demonstrated that in patients with AMI, IMA measured 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.

Other clinical applications of IMA

There have been reports that increases in IMA may also reflect conditions other than cardiac ischemia (Roy et al. 2004b, c, d, Borderie et al. 2004, Can et al. 2006, Falkensammer et al. 2007, Sbarouni et al. 2009, 2010). Moreover, some evidence suggests that IMA levels might be used in the diagnosis of pulmonary embolism (Turedi et al. 2009). There are only two studies in the literature

about the use of IMA for diagnostic purposes in pulmonary embolism. Turedi et al. (2007) examined the serum IMA levels of 60 individuals, consisting of 30 patients with pulmonary embolism and 30 healthy individuals, and demonstrated that IMA levels were significantly higher than those in healthy individuals in 97% of patients. Recently, the same group demonstrated that IMA levels may be useful as a discriminative marker to exclude pulmonary embolism in consecutive patients presenting to the ED (Turedi et al. 2008).

Investigators have also reported IMA to be a sensitive measure of the magnitude and duration of ischemia induced during percutaneous coronary intervention (Quiles et al. 2003, Sinha et al. 2003). A subsequent percutaneous coronary intervention study supported this finding and also demonstrated a greater increase in IMA level from baseline in patients without collateral coronaryartery circulation than in those with it (Garrido et al. 2004).

Similarly, a decrease in IMA values has been documented after muscle ischemia (Zapico-Muñiz et al. 2004, Roy et al. 2004b). It has been demonstrated that an increase in lactate concentration, which occurs after a forearm ischemia test, decreases true IMA values and therefore the diagnostic sensitivity. Clinicians must be careful when interpreting IMA negative values in patients with sepsis and renal failure, all of which are associated with increased lactate concentrations (Pantazopoulos et al. 2009). In patients with type 2 diabetes mellitus who demonstrate poor glycaemic control have higher IMA concentrations than those with good glycaemic control (Piwowar et al. 2008).

Conclusion

Many questions about IMA remain unanswered. Although the main limitation of IMA at present is its low specificity, it may be a useful test to rule out ACS from low to moderate pre-test probability conditions with negative cardiac troponins and a negative ECG. For efficient provision of care in the ED, a high negative predictive value may be most critical, for while false negatives are undesirable, true negatives are of greater importance, because the correct exclusion of myocardial infarction preserves limited and expensive resources. A test like IMA may be enormously valuable to the emergency physician assessing chest pain patients but we require a better understanding on this marker before it is ready for prime time use.

Further studies are required to investigate the role of IMA in cardiac ischemic diseases in the ED setting. An example is the large multicentre, randomised, controlled trial evaluating the utility of IMA for risk stratification in 1250 patients presenting with chest discomfort and possible ischemic heart disease, and evaluating the diagnosis and prognostic implication of IMA for major adverse cardiac events (the IMAgine trial –NCT00355992). This will probablyprovide a definitive answer.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Anwaruddin S, Januzzi JLJr, Baggish AL, Lewandrowski EL, Lewandrowski KB. (2005). Ischemia modified albumin improves the usefulness of standard cardiac biomarkers for the diagnosis of myocardial ischemia in the emergency department setting. *Am J ClinPathol* 123:140–5.

Aparci M, Kardesoglu E, Ozmen N, Ozcan O, Cebeci BS, Cingozbay BY, Dincturk M. (2007). Prognostic significance of ischemia-modified albumin in patients with acute coronary syndrome. *Coron Artery Dis* 18:367–73.

Apple FS, Wu AH, Mair J, Ravkilde J, Panteghini M, Tate J, Pagani F, Christenson RH, Mockel M, Danne O, Jaffe AS; Committee on Standardization of Markers of Cardiac Damage of the IFCC. (2005). Future biomarkers for detection of ischemia and risk stratification in acute coronary syndrome. *ClinChem* 51: 810–24.

Bar-Or D, Lau E, Winkler JV.(2000). Novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia -a preliminary report.*J Emerg Med* 19:311–15.

Beetham R, Monk C, Keating L, Benger JR, Kendall J.(2006). Effects of storage at – 20 degrees C on ischemia-modified albumin results. *Ann ClinBiochem*43:500–2.

Bhagavant NV, Lai EM, Rios PA, Yang J, Ortega-Lopez AM, Shinoda H, Honda SAA, Rios CN, Sugiyama CE, Ha CE. (2003). Evaluation on human serum albumin cobalt binding assay for the assessment of myocardial ischemia and myocardial infarction. *Clin Chem* 49:581–5.

Borderie D, Allanore Y, Meune C, Devaux JY, Ekindjian OG, Kahan A. (2004). High ischemia-modified albumin concentration reflects oxidative stress but not myocardial involvement in systemic sclerosis. *ClinChem* 50:2190–3.

Can M, Demirtas S, Polat O, Yildiz A. (2006). Evaluation of effects of ischaemia on the albumin cobalt binding (ACB) assay in patients exposed to trauma. *Emerg Med J* 23:537–9.

Christenson RH, Azzazy HME. (1998). Biochemical markers of the acute coronary syndromes. *ClinChem* 44:1855–64.

Christenson RH, Duh SH, Sanhai WR, Wu AH, Holtman V, Painter P, Branham E, Apple FS, Murakami M, Morris DL. (2001). Characteristics of an Albumin Cobalt Binding Test for assessment of acute coronary syndrome patients: a multicenter study. *ClinChem* 47:464–70.

Collinson PO, Gaze DC. (2007). Biomarkers of cardiovascular damage.*Med PrincPract* 16:247–61.

Collinson PO, Gaze DC, Bainbridge K, Morris F, Morris B, Price A, Goodacre S. (2006). Utility of admission cardiac troponin and 'Ischemia Modified Albumin' measurements for rapid evaluation and rule out of suspected acute myocardial infarction in the emergency department. *Emerg Med J* 23:256–61.

Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia-Gonzalez MJ, Samimi-Fard S, Kaski JC. (2008a). Relation of ischemia-modified albumin levels and left ventricular systolic function in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *ClinChimActa* 388:196–9.

Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia-Gonzalez MJ, Samimi-Fard S, Reiter RJ, Kaski JC. (2008b). Association of

ischemia-modified albumin and melatonin in patients with ST-segment elevation myocardial infarction. *Atherosclerosis* 199:73–8.

Dominguez-Rodriguez A, Abreu-Gonzalez P, Jimenez-Sosa A, Samimi-Fard S, Idaira HB. (2009a). Does ischemia-modified albumin add prognostic value to the Thrombolysis In Myocardial Infarction risk score in patients with ST-segment elevation myocardial infarction treated with primary angioplasty? *Biomarkers* 14:43–8.

Dominguez-Rodriguez A, Kaski JC, Abreu-Gonzalez P, Samimi-Fard S. (2009b). Role of ischemia modified albumin to ST-segment resolution after mechanical reperfusion in patients with ST-segment elevation myocardial infarction. *Atherosclerosis* 203:576–80.

Duseja R, Feldman JA. (2004). Missed acute cardiac ischemia in the ED: limitations of diagnostic testing. *Am J Emerg Med* 22:219–25.

Fagan GJ, Wayment H, Morris DL, Crosby PA. (2002). The albumin cobalt binding test: analytical performance of a new automated chemistry assay for the detection of ischemia modified albumin (IMA). *J Clin Ligand Assay* 25:178–87.

Falkensammer J, Stojakovic T, Huber K, Hammerer-Lercher A, Gruber I, Scharnagl H, Fraedrich G, Santner W, Schocke M, Greiner A. (2007). Serum levels of ischemia-modified albumin in healthy volunteers after exercise-induced calf-muscle ischemia. *ClinChem Lab Med* 45:535–40.

Garrido IP, Roy D, Calviño R, Vazquez-Rodriguez JM, Aldama G, Cosin-Sales J, Quiles J, Gaze DC, Kaski JC. (2004). Comparison of ischemia-modified albumin levels in patients undergoing percutaneous coronary intervention for unstable angina pectoris with versus without coronary collaterals.*Am J Cardiol* 93:88–90.

Gaze DC. (2009). Ischemia modified albumin: a novel biomarker for the detection of cardiac ischemia. *Drug MetabPharmacokinet* 24:333–41.

Gaze DC, Crompton L, Collinson P. (2006). Ischemia-modified albumin concentrations shuold be interpreted with caution in patients with low serum albumin concentrations. *Med PrincPract* 15:322–4.

Gidenne S, Ceppa F, Fontan E, Perrier F, Burnat P. (2004). Analytical performance of the albumin cobalt binding (ACR®) test on the cobas MIRA® plus analyzer. *ClinChem Lab Med* 42:455–61.

Govender R, De Greef J, Delport R, Becker PJ, Vermaak WJ. (2008). Biological variation of ischemia-modified albumin in healthy subjects. *Cardiovasc J Afr* 19:141–4.

Hakligor A, Kosem A, Senes M, Yucel D. (2010). Effect of albumin concentration and serum matriz on ischemia-modified albumin. *ClinBiochem* 43:345–8.

Hjortshøj S, Kristensen SR, Ravkilde J. (2010). Diagnostic value of ischemia-modified albumin in patients with suspected acute coronary syndrome. *Am J EmergMed* 28:170–6.

Iuliano L, Pratico D, Greco C, Mangieri E, Scibilia G, FitzGerald GA, Violi F. (2001). Angioplasty increases coronary sinus F2-isoprostane formation: evidence for *in vivo* oxidative stress during PTC. *J Am CollCardiol* 37:76–80.

Jalan R, Schnurr K, Moorkerjee RP, Chshire L, Hodges S, Muravsky V, Williamns R, Matthes G, Davies NA. (2009). Alteration in the functional capacity of albumin in patients with decompensated cirrhosis is associated with increase mortality. *Hepatology* 50:555–64.

Keating L, Benger JR, Beetham R, Bateman S, Veysey S, Kendall J, Pullinger R. (2006). The PRIMA study: presentation ischaemia-modified albumin in the emergency department. *Emerg Med J* 23:764–8.

Lee YW, Kim HJ, Shin HB, Choi TY, Lee YK. (2007). Application of albumin-adjusted ischemia modified albumin index as an early screening marker for acute coronary syndrome.*ClinChimActa* 384:24–7.

Libby P. (2001). Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* 104:365–72.

Lippi G, Montagnana M, Guidi GC. (2006a). Albumin cobalt binding and ischemia modified albumin generation: an endogenous response to ischemia? *Int J Cardiol* 108:410–11.

Lippi G, Montagnana M, Salvagno G, Guidi GC. (2006b). Potential value for new diagnostic markers in the early recognition of acute coronary syndromes. *CJEM* 8:27–31.

Lippi G, Montagnana M, Salvagno G, Guidi GC. (2007). Standarization of ischemia-modified-albumin testing: adjunstement for serum albumin. *ClinChem Lab Med* 45:261–2.

Ming-Hui Lin R, Fatovich DM, Grasko JM, Vasikaran SD. (2010). Ischaemia modified albumin cannot be used for rapid exclusion of acute coronary syndrome. *Emerg Med J* [Epub ahead of print].

Morrow DA, de Lemos JA, Sabatine MS, Antman EM. (2003). The search for a biomarker of cardiac ischemia. *Clin Chem* 49:537–9.

Pantazopoulos I, Papadimitriou L, Dontas I, Demestiha T, Lakovidou N, Xanthos T. (2009). Ischaemia modfied albumin in the diagnosis of acute coronary syndromes. *Resuscitation* 80:306–10.

Peacock F, Morris DL, Anwaruddin S, Christenson RH, Collinson PO, Goodacre SW, Januzzi JL, Jesse RL, Kaski JC, Kontos MC, Lefevre G, Mutrie D, Sinha MK, Uettwiller-Geiger D, Pollack CV. (2006). Meta-analysis of ischemia-modified albumin to rule out acute coronary syndromes in the emergency department. *Am Heart J* 152:253–62.

Piwowar A, Knapik-Kordecka M, Warwas M. (2008). Ischemia-modified albumin level in type 2 diabetes mellitus – Preliminary report. *Dis Markers* 24:311–17.

Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, Griffith JL, Selker HP. (2000). Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med* 342:1163–70.

Quiles J, Roy D, Gaze D, Garrido IP, Avanzas P, Sinha M, Kaski JC. (2003) Relation of ischemia-modified albumin (IMA) levels following elective angioplasty for stable angina pectoris to duration of balloon-induced myocardial ischemia. *Am J Cardiol* 92:322–4.

Rajappa M, Sharma A. (2005). Biomarkers of cardiac injury: an update. *Angiology* 56:677–91.

Roy D, Quiles J, Aldama G, Sinha M, Avanzas P, Arroyo-Espliguero R, Gaze D, Collinson P, Carlos Kaski J. (2004a). Ischemia modified albumin for the assessment of patients presenting to the emergency department with acute chest pain but normal or non-diagnostic 12-lead electrocardiograms and negative cardiac troponin T. *Int J Cardiol* 97:297–301.

Roy D, Quiles J, Sharma R, Sinha M, Avanzas P, Gaze D, Kaski JC. (2004b). Ischemia-modified albumin concentrations in patients with peripheral vascular disease and exercise-induced skeletal muscle ischemia. *ClinChem* 50:1656–60.

Roy D, Quiles J, Sinha M, Aldama G, Gaze D, Kaski JC. (2004c). Effect of direct-current cardioversion on ischemia-modified albumin levels in patients with atrial fibrillation. *Am J Cardiol* 93:366–8.

Roy D, Quiles J, Sinha M, Floros D, Gaze D, Collinson P, Baxter GF, Kaski JC. (2004d). Effect of radiofrequency catheter ablation on the biochemical marker ischemia modified albumin. *Am J Cardiol* 94:234–6.

Ryan TJ, Anderson JL, Antman EM, Braniff BA, Brooks NH, Califf RM, Hillis LD, Hiratzka LF, Rapaport E, Riegel BJ, Russell RO, Smith EE Jr, Weaver WD. (1996). ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Managementof Acute Myocardial Infarction). *J Am CollCardiol* 28:1328–428.

Sbarouni E, Georgiadou P, Panagiotakos D, Alivizatos PA, Voudris V. (2009). Increased ischaemia modified albumin following coronary artery bypass grafting. *Biomarkers* 14:38–42.

Sbarouni E, Georgiadou P, Manginas A, Panagiotakos D, Karavolias GK, Voudris V. (2010). Ischaemia-modified albumin in pulmonary hypertension. *Biomarkers* 15:238–42.

Sinha MK, Gaze Dc, Tippins JR, Collinson PO, Kaski JC. (2003). Ischemia modified albumin is a sensitive marker of myocardial ischemia after percutaneous coronary intervention. *Circulation* 107:2403–5.

Sinha MK, Roy D, Gaze DC, Collinson PO, Kaski JC. (2004). Role of "ischemia modified albumin", a new biochemical marker of myocardial ischemia, in the early diagnosis of acute coronary syndromes. *Emerg Med J* 21:29–34.

Sinha MK, Vasquez JM, Calvino R, Gaze DC, Collinson PO, Kaski JC. (2006). Effects of balloon occlusion during

percutaneous coronary intervention on circulating ischemia modified albumin and transmyocardial lactate extraction. *Heart* 92: 1852–3.

Storrow AB, Gibler WB. (2000). Chest pain centers: diagnosis of acute coronary syndromes. *Ann Emerg Med* 35:449–61.

Toutouzas K, Stefanadis C. (2006). Advances in vulnerable plaque detection and treatment: how far have we gone? *Hellenic J Cardiol*47:129–31.

Turedi S, Gunduz A, Mentese A, Karahan SC, Yilmaz SE, Eroglu O, Nuhoglu I, Turan I, Topbas M. (2007) Value of ischemia-modified albumin in the diagnosis of pulmonary embolism. *Am J Emerg Med* 25:770–3.

Turedi S, Gunduz A, Mentese A, Topbas M, Karahan SC, Yeniocak S, Turan I, Eroglu O, Ucar U, Karaca Y, Turkmen S, Russell RM. (2008). The value of ischemia-modified albumin compared with d-dimer in the diagnosis of pulmonary embolism. *Respir Res* 9:49.

Turedi S, Patan T, Gunduz A, Mentese A, Tekinbas C, Topbas M, Karahan SC, Yulug E, Turkmen S, Ucar U. (2009). Ischemia-modified albumin in the diagnosis of pulmonary embolism: an experimental study. *Am J Emerg Med* 27:635–40.

Van Belle E, Dallongeville J, Vicaut E, Degrandsart A, Baulac C, Montalescot G;, OPERA Investigators. (2010). Ischemia-modified albumin levels predict long-term outcome in patients with acute myocardial infarction. The French Nationwide OPERA study. *Am Heart J* 159:570–6.

Worster A, Devereaux PJ, Heels-Ansdell D, Guyatt GH, Opie J, Mookadam F, Hill SA. (2005). Capability of ischemia-modified albumin to predict serious cardiac outcomes in the short term among patients with potential acute coronary syndrome. *CMAJ* 172:1685–90.

Zapico-Muñiz E, Santaló-Bel M, Mercé-Muntañola J, Montiel JA, Martínez-Rubio A, Ordóñez-Llanos J. (2004). Ischemia-modified albumin during skeletal muscle ischemia. *Clin Chem* 50:1063–5.