Ischemia Modified Albumin as an Acute-Phase Reactant

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Ischemia is a common underdiagnosed vascular emergency, which is associated with an adverse prognosis. It is initiated whenever the arterial flow cannot supply sufficient oxygen resulting to irreversible damage and cell death. The clinical assessment is essential for the timely diagnosis and intervention of this disorder. Yet, no laboratory test for ischemia is available for the diagnosis of this clinically challenging situation.

Ischemia-modified albumin (IMA) is regarded as a new sensitive marker of myocardial ischemia, in contrast to cardiac enzymes which are released when cardiac necrosis occurs. During an acute ischemic event, structural changes occur in the amino terminus of albumin, rapidly reducing its capacity to bind transition metal ions and generate a metabolic variant of the albumin referred as IMA.

Albumin, the most abundant serum protein with a mean concentration of 0.63 mmol/L, is a powerful acute phase reactant as it changes dramatically during vascular injury and inflammatory processes. Albumin acts as a buffering agent for endogenous or exogenous toxic molecules due to its various ligands binding ability. The biochemical mechanisms modifying the amino-terminal region of albumin during ischemia are unclear, but reperfusion after an ischemic event may damage serum albumin as much as, if not more than, ischemia itself. Accumulating evidence support that IMA is also produced in the clinical setting of ischemia-reperfusion conditions with excessive oxidative stress state, like those observed in thrombolytic therapy, coronary intervention and open-heart surgery.

Hypoxia, acidosis, energy dependent disruptions or free radical damage have been proposed to be involved in the conversion of albumin to IMA, most of which occur within minutes. IMA is approximately 1% to 2% of the total albumin concentration and increases to 6% to 8% in patients experiencing ischemia. IMA rises within six to 10 minutes, seems to be produced continually during the acute phase of vascular injury and remains elevated during an ischemic event. IMA has a short half-life returning to normal in 6–12 hours, as shown in patients undergoing elective percutaneous coronary intervention.

IMA was studied primarily as a diagnostic marker in selected populations with acute coronary syndromes (ACS). IMA measurements have demonstrated high sensitivity of detecting even subclinical myocardial ischemia and strong predictive power of subsequent cardiac troponin results in ACS patients. However, IMA may increase in conditions of non cardiac ischemia, such as skeletal muscle, cerebral, pulmonary and gastrointestinal ischemia and in diseases which are potent producers of free radicals, such as liver cirrhosis, infections and advanced neoplasms. Therefore, the specificity of IMA concentrations in the detection of cardiac ischemia is quite limited.

To date, there is only one study in the literature about the use of IMA for diagnostic purposes in acute aortic dissection (AOD). Several mechanisms can be employed to support this concept. First of all, AOD is a typical model of supply mismatch which could stimulate the synthesis of IMA. AOD usually spreads from diseased segments of the aortic wall in either an antegrade or a retrograde fashion, causing malperfusion syndrome by dynamic or static obstruction of the coronaries to iliac arteries.

Cerebrovascular manifestations, limb ischemia, recurrent abdominal pain or renal failure are commonly caused by involvement of a side-branch orifice into the dissection. Moreover, patients with AOD may be haemodynamically unstable with generalised tissue hypoxia, which could also contribute to elevated IMA levels. Second, patients with AOD often present with abnormal electrocardiographic findings and positive troponin values indicating various degrees of myocardial involvement-ischemia or infarction- due to reduction of coronary blood flow. Third, AOD is associated with a succession of ischemic-reperfusion episodes triggering a vicious circle of oxidative regeneration and damage, which could be reflected by high IMA concentrations.
Recent reports have shown that IMA production also depends on reperfusion-induced events, affecting not only myocardium but any organ. Last but not least, AOD is considered as a syndrome of marked and prolonged acute phase response followed by the enhanced release of relative reactants, like albumin, C-reactive protein (CRP) and lactate dehydrogenase; IMA could be released in similar manner. Intriguingly, IMA was not found to differ among patients with AOD at 23 ± 17 hours from symptom onset (93±19 U/ml) compared to patients with chronic aneurysms (90±14 U/ml) or normal controls (91±9 U/ml). The simplest explanation is related to the IMA kinetics. It is possible that the opportune time window to detect IMA was missed. Further investigations are required to validate the diagnostic value of IMA in this disorder with earlier timing for IMA samples (within 6-12 hours). There are also confounding analytical issues regarding the use of IMA assay- the albumin-cobalt binding (ACB) test. The determinants of the performance of the ACB test are not yet fully elucidated and data exist suggesting that plasma pH, plasma cysteine/cystine ratio and the oxidation of cys34 of albumin could also influence IMA results and particularly in this condition.

Nevertheless, positive relationships were observed between IMA on admission and CRP as well as between IMA and time from symptom onset. These findings suggest that IMA concentrations may change in response to elevated CRP levels that occur during the acute phase of vascular injury in AOD. It is of note that IMA, as an index of the preceding ischemia, was positively correlated with cardiac enzymes, which represent the extent of the subsequent myocardial necrosis.

IMA has been evaluated post-operatively in both non-cardiac and cardiac surgical patients with contradictory results. IMA did not increase following surgical repair in AOD patients; likewise no significant difference was observed in albumin. However, our group has shown that after coronary bypass surgery, IMA levels were significantly elevated with an immediate peak post-operatively and remained considerably higher compared to baseline values. In this study, IMA changes were independent of albumin variation, which was significantly decreased following surgery. In non-cardiac surgery, postoperative IMA increase was associated with lower postoperative albumin concentrations.

During operative procedures, the excess volume shifts and the administration of fluids could influence albumin levels and subsequently, IMA measurement. Data exist suggesting that serum albumin concentrations and the presence of lactic acidosis could interfere with the performance of the ACB test. Recently, it has been published that the primary predictor of IMA in serum matrix is albumin concentration.

Two different applications have been proposed to eliminate the effect of albumin concentration on IMA: 1) the use of a calculated albumin-adjusted IMA index = serum albumin concentration (g/dl) x 23 + IMA (U/ml)-100 and 2) adjusting the results by use of median albumin values of the population [(individual serum albumin concentration /median albumin concentration of the population) xIMA] 30,31,32. The optimum cutoff ACB test value has not yet been determined. It should be taken into account that surgery is too variable to be expressed for the optimal application.

Several surgical issues may confound the interpretation of IMA results in such conditions. Perioperative and postoperative myocardial ischemia, due to manipulation of the heart, inadequate myocardial protection, reperfusion injury and incomplete revascularization, can occur to varying degrees, after cardiac surgery and can be early identified by IMA23,24. After surgery, there might be a baseline release of acute phase reactants due to the heart injury caused by the surgical procedure itself, thus the damage is different from that in patients with naturally occurring disease. Any additional release into the circulation may be due to a perioperative myocardial infarction or a higher degree of vascular injury that is indicative of future adverse events. In AOD, acute flow obstructions may lead to necrosis without proceeding ischemia and may result in limiting the access of the modified albumin to the systemic circulation as well as its exposure to circulating free radicals.

To conclude, IMA, as a biochemical by-product of albumin changes, may participate in the acute phase reaction induced by vascular injury. In this concept, IMA could be a useful tool for the early recognition of AOD syndrome. Although our study did not demonstrate any benefits, this should not discourage future trials, particularly since there appears to be a link to the pathophysiology of this disease. Ensuring appropriate time sampling and a clear understanding of the mechanism of IMA production, is essential to improve its clinical utility in such medical and surgical conditions. Clearly, further studies are required to confirm the novel hypothesis we have identified in our study.

REFERENCES

REFERENCES (Continued)


