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Ischemia-Modified Albumin: Its Diagnostic Implications and Shortfalls

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Abstract

Patients presenting with chief complaint of chest pain or other signs suggestive of acute coronary syndrome (ACS) in hospital is often time-consuming, expensive and problematic to arrive to the definitive diagnosis for the cause of chest pain. Recent research has found that ischemia-modified albumin (IscMA) is an ideal biomarker for ischemia. It is highly sensitive and detectable in the early phase of ACS. Many clinical studies have demonstrated that IscMA can be used for early diagnosis of acute myocardial infarction (AMI), so that the admission rate of non-ischemic patients can be reduced allowing the relieve from the heavy cost burdened on admission to Intensive Coronary Care Unit (ICCU). Ischemia modified albumin which is proposed biomarker for myocardial ischemia is detected within six to ten minutes and remains elevated for up to several hours later. Although, it was thought as an evident biomarker for ischemia process in AMI and ACS, but it's no doubt that the elevations are also accompanied in various other diseases where the process of ischemia occurs. Studies have surfaced the elevation of IscMA is other diseases too, namely diabetes, hypertension, in smokers, in patients with peripheral vascular disease, skeletal muscle ischemia, end stage renal disease, in cirrhosis of liver, systemic sclerosis, etc. It is the right time to unveil the exact mechanisms of elevation of IscMA which is accompanied in various diseased states.

Key words: chest pain, ischemia-modified albumin, acute myocardial infarction, acute coronary syndrome, troponin.

Patients presenting with chief complaint of chest pain or other signs suggestive of acute coronary syndrome (ACS) in hospital is often time-consuming, expensive and problematic to arrive to the definitive diagnosis for the cause of chest pain [1]. Millions of patients with chest pain present annually to hospital and nursing homes potentially indicative of ischemia [2]. Recent research has found that ischemia-modified albumin (IscMA) is an ideal biomarker for ischemia [3]. Till date the Quantitative or qualitative determination cardiac troponin I or T (cTnI or cTnT) has been well accepted as a marker of myocardial damage, but most of these markers are negative in acute myocardial infarction, such as unstable angina (UA) [2]. However, these biomarkers are products of myocardial necrosis, and thus are detected typically at a later stage of myocardial damage [4]. When ultimately a positive marker is found/evaluated, it is often too late to take remedial /rescue measures at the right time. It is the call of time and decision making as early as possible in patients with ACS and it must be done before irreversible damage had occurred or in a condition when there is no cell death. Clinically, we therefore, need a relevant and early biomarker for judging myocardial ischemia at an early stage [5]. On the timeline, the advent of IscMA has been implicated as the most appropriate serum biomarker of cardiac ischemia. It is highly sensitive and detectable in the early phase of ACS [6]. Many clinical studies have demonstrated that IscMA can be used for early diagnosis of acute myocardial infarction (AMI), exclusion of ACS and risk stratification of ACS [7], so that the admission rate of non-ischemic patients and misdiagnosis can be reduced along with the heavy cost burden on the patient on their admission to Intensive Coronary Care Unit (ICCU) [1]. Thus the ideal role of an ischemia marker would be therefore to rule-out for acute myocardial infarction. The most logical place to use such test is therefore in emergency department (ED).

What is ischemia-modified albumin?

The N-terminal residues of human serum albumin are known to be a binding site for transition metal ions, where cobalt, nickel and copper. Most probably as a result of hypoxia, acidosis, free-radical injury, and energy-dependent membrane disruption, the N-terminal residues undergo a decrease in binding capacity in the presence of ischemia. The estimation of IscMA is so simple that it can be even done in laboratory with very basic facilities or say even in bedside. The alterations can be measured by addition of a known amount of cobalt to patient's serum. The amount of free cobalt which remain in the mixture, which cannot bind to albumin due to its alteration in N-terminal binding residue, is used for binding to Dithiothreitol (DTT) and the color developed due to binding of DTT with cobalt is measured using colorimeter at 470nm [1].

So depending on the extent of damage in the N-terminal residue the binding of albumin to cobalt varies and it is also known that human albumin is less stable than of other species. So if one tries to mimic the similar conditions of ischemic process with albumin obtained from other species, it would not work in similar fashion.

Ischemia modified albumin which is proposed biomarker for myocardial ischemia is detected within six to ten minutes and remains elevated for up to several hours later as an acute phase of vascular injury thus allowing detection before the development of myocardial necrosis, which is evidently observed by the levels of creatine kinase isoenzyme (CK-MB), troponin and myoglobin [8]. Ischemia modified albumin is approximately 1% to 2% of the total circulating albumin and increases to 6% to 8% in patients experiencing ischemia.

Modifications of IscMA in human albumin

By combination of nuclear magnetic resonance spectroscopy, HPLC and liquid chromatography combined with mass spectrophotometry, it is now confirmed that the N- terminal aspartate-alanine-histidine- lysine sequence binds cobalt and alteration/modification of this site affects the binding potential of human albumin to cobalt [9]. It is predicted that, at times of oxidative stress, there is a release of copper II from weak binding sites of circulating proteins and peptides. In the presence of a reducing agent such as ascorbic acid, free copper II is converted to copper I, which furthermore react with oxygen to form copper II and generate superoxide free radicals. The free copper II ions released can be scavenged by circulating albumin but they are tightly bound to the N-terminus [10]. Copper-bound albumin is than damaged by hydroxyl free radicals, causing removal of the three N-terminal amino acids and release of the copper II ion to repeat the process of chain reaction. Thus the apparent rapid rise in IscMA occurs following ischemia.

Ischemia-modified albumin shortfalls

Studies on patients with increased IscMA, the N-terminal portion of albumin was sequenced in some cases and no evidence of N-terminal degradation or truncation was found. Some other explanations have been sought with respect to the drastic rise in IscMA. They explained that when the fatty acids are released in myocardial ischemia, it binds with the albumin at its binding sites, preventing albumin from binding to cobalt, hence account for the presence of IscMA, even though IscMA is not present.

Although, it was thought as an evident biomarker for ischemia process in AMI and ACS, but it's no doubt that the elevations are also accompanied in various other diseases where the process of ischemia occurs. Studies have surfaced the elevation of IscMA is other diseases too, namely diabetes, hypertension, smokers, patients with peripheral vascular disease, skeletal muscle ischemia, end stage renal disease, cirrhosis of liver, systemic sclerosis to name few in the list.

What needs to be unveiled?

Although it is established that IscMA is elevated following ischemia, but the exact mechanism is unknown as the hypothetical assumption of truncation or damage of N-terminal residues so that the binding of cobalt is prevented leaving behind the cobalt as free form to react with DTT and thus forming the end colored complex. As the binding of cobalt with albumin occurs but still we need to explore the possibilities of cobalt binding to the human albumin, though mentioned that it can bind only to N-Terminal sites.

Secondly, does fatty acid binding to albumin prevents the binding of the cobalt still need to be unveiled.

It is always necessary that only in ischemia there is a rapid rise of IscMA. Though several disease states have observed a closer association in the rise of IscMA, but the exact mechanisms needs to be unveiled. Is it due to ischemia in all the diseases which is solely responsible for the up rise in IscMA or is there any evident mechanisms behind their elevations? We need to attend the mechanism in each of these diseases, where it is accompanied by the rise of IscMA so that in future we can use IscMA is more broader way and not limiting its role only in acute myocardial infarction and in risk stratifications in acute coronary syndrome.

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