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The clinical significance of ischaemia-modified albumin in acute coronary syndrome and hypertension

Guoyan Pan[1], Jinzao Chen[1], Congying Lv[2], Xueping Lin[1], Junwei Huang[1], Bin Lin[1] and Zhiwei Wu[1]

[1]Department of Cardiology, The First Hospital of Putian City, Putian, China and [2]Department of Internal Medicine, Licheng District Hospital of Putian, Putian, China

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Corresponding author:
Zhiwei Wu;
Email: wuzhiwei_wongkakui@126.com

G.P., J.C. and C.L. are first authors.

Abstract

Background: Early diagnosis of acute coronary syndrome is more and more important because of its mortality and morbidity. Hypertension is one of the pathogenesis of acute coronary syndrome, which often leads to stenosis and ischaemia. Ischaemia-modified albumin is sensitive for the occurrence of ischaemia, which attracted us in the significance of ischaemia-modified albumin in patients with chest pain, especially patients complicated with hypertension. *Methods:* In total, 200 patients with acute chest pain were included in the study. According to the diagnostic criteria, patients were divided into acute coronary syndrome group and non-ischaemic chest pain group. Cardiac biomarkers were measured with 30 minutes in emergency department, including cardiac troponin T, creatine kinase MB, and ischaemia-modified albumin. Receiver operating characteristic curve (ROC) analysis was used for the sensitivity and specificity of ischaemia-modified albumin in the early diagnosis of acute coronary syndrome. Comparisons between ischaemia-modified albumin and cardiac Troponin T were done between groups. *Results:* The demographics in two groups were not significantly different in most aspects. Compared with non-ischaemic chest pain group, serum levels of ischaemia-modified albumin and cardiac Troponin T were significantly higher in acute coronary syndrome group. ROC analysis showed that ischaemia-modified albumin had a good sensitivity and specificity in early diagnosis of acute coronary syndrome. The level of ischaemia-modified albumin in acute coronary syndrome patients with hypertension was higher than that in non-ischaemic chest pain patients. *Conclusions:* In patients complained with acute chest pain, the serum measurement of ischaemia-modified albumin is potential valuable for the early diagnosis of acute coronary syndrome, especially combined with ECG. The serum level of ischaemia-modified albumin in acute coronary syndrome patients is significantly associated with hypertension.

Introduction

ST-elevation myocardial infarction and non-ST-elevation myocardial infarction are two different types of acute myocardial ischaemia or heart attack that differ primarily in ECG changes, clinical manifestations, and treatment strategies. ST-elevation myocardial infarction presents with ST-segment elevation in the ECG, usually greater than 1 mm, whereas non-ST-segment elevation myocardial infarction presents with ST-segment depression, inverted T-waves, or no significant ECG changes. Clinically, ST-elevation myocardial infarction patients usually experience severe chest pain with other symptoms, while non-ST-segment elevation myocardial infarction patients may have miler or atypical symptoms. ST-elevation myocardial infarction requires emergency reflow treatment, while non-ST-segment elevation myocardial infarction determines a treatment strategy based on a patient's risk assessment, including medication and possible interventional procedures, both of which require prompt medical intervention. Coronary atherosclerotic heart disease from stable angina pectoris to myocardial infarction is a continuous pathological process, and studies have found that there are also minor myocardial damage caused by microthrombus in the unstable angina pectoris (UAP) stage, of course, not all patients with stable angina pectoris will develop acute coronary syndrome.[1,2] Cardiovascular diseases, especially acute coronary syndrome, have become a leading cause of death and morbidity worldwide, and early diagnosis of patients with chest pain has become increasingly urgent. Clinically, common cardiac biomarkers, including creatine kinase MB and troponin levels, typically show large elevations about 3–6 hours after cardiomyocyte injury occurs, and hypersensitive troponin can be detected up to an hour after myocardial injury.[3] Measurement of troponin is very important. Typically, myocardial infarction results in the death of heart muscle cells, releasing biomarkers such as troponin into the bloodstream. Therefore, when a patient presents with typical or atypical angina symptoms, and troponin levels are elevated, the doctor is highly suspicious of non-ST-segment elevation myocardial infarction and further confirms the diagnosis. In the diagnosis of ST-elevation

myocardial infarction, although an elevation of troponin usually occurs, the primary determinant of diagnosis is the apparent ST-segment elevation on the ECG. This characteristic change on the ECG is often sufficient to establish a diagnosis of ST-elevation myocardial infarction, so troponin levels do not need to be relied upon to confirm the diagnosis in the case of ST-elevation myocardial infarction.[4]

In recent years, a new indicator has been demonstrated the potential early diagnostic significance for acute coronary syndrome, which is called ischaemia-modified albumin. Ischaemia-modified albumin is a form of human serum albumin in which the N-terminal amino acids have been modified by ischaemia. Ischaemia-modified albumin is a protein, usually albumin in blood plasma, that is altered by ischaemia (lack of blood supply). Ischaemia results in insufficient oxygen in cells, which can alter the structure of the albumin molecule. This change allows albumin to form more chemical bonds with metal ions (usually nickel) in laboratory tests, so the ischaemia-modified albumin test can be used to detect the presence of ischaemia. This modification reduces the capacity of plasma albumin to bind to heavy metal ions such as cobalt.[5] The level of ischaemia-modified albumin is normally distributed in healthy population, and it is not affected by age, gender, race, or smoking.[6] Ischaemia-modified albumin, as an ideal biomarker for early diagnosis of acute myocardial ischaemia, has received extensive attention and research. Ischaemia-modified albumin can be elevated in other ischaemic conditions, not just myocardial infarction. Therefore, it is mainly used to screen patients with possible ischaemic disease, rather than to diagnose myocardial infarction. In summary, ischaemia-modified albumin is a biomarker used to detect ischaemia, but it is a different concept from acute myocardial infarction, which often requires the use of more specific markers to confirm the diagnosis. In clinical practice, ischaemia-modified albumin can be used to help assess a patient's cardiovascular risk and in conjunction with other tests for a comprehensive history assessment. Bar-OR et al showed increased ischaemia-modified albumin levels in acute coronary syndrome patients, which are detectable before the subsequent increases in the other biomarkers.[7] Sinha MK's study revealed that ischaemia-modified albumin levels rise up for just 5–10 minutes after the onset of myocardial ischaemia, which provides the possibility for the early detection of acute coronary syndrome.[8] Several other studies reported the potential value of ischaemia-modified albumin in the early diagnosis, risk stratification, and prognosis evaluation in acute coronary syndrome.[9,10] In addition, American Food and Drug Administration has approved the use of ischaemia-modified albumin in the exclusive diagnosis of acute coronary syndrome in 2003.

Though numerous studies have been done about the significance of ischaemia-modified albumin in acute ischaemia, few researchers focused on the value of ischaemia-modified albumin in other diseases, especially those may lead to arteriosclerosis and ischaemia, like hypertension and diabetes mellitus.

There is increasing evidence that not only the elevation of blood pressure but also the increase in blood pressure variability is associated with hypertensive vascular damages, which will result in cardiovascular events.[11] Abnormal blood pressure affects the vascular endothelial function, breaks vascular elasticity, and leads to ischaemic changes. We have investigated the association between ischaemia-modified albumin and blood pressure and revealed its predictive significance in hypertensive tissue damage in previous study.[12] The result drew the attention of us in the concentration difference of ischaemia-modified albumin in acute coronary syndrome patients with or without hypertension. Meanwhile, we also aimed to investigate the increase of ischaemia-modified albumin in acute coronary syndrome patients.

Methods

Study population

From July 2021 to February 2022, patients originally admitted to our emergency department with complaints suggestive of acute myocardial ischaemia evolving within 6 hours were examined for the primary inclusion, including chest pain or heaviness, syncope, palpitations, and other similar symptoms (shortness of breath, cold sweat, nausea). This study was conducted in the clinical laboratory department, cardiology department and emergency Department of Putian First Hospital, The First Hospital of Putian. Our study was approved by the institutional ethics committee. Each enrolled patient signed an informed consent form for the use of related data. The exclusion criteria included: 1) Patients with complaints lasting for more than 6 hours or complaints had vanished for over 2 hours; 2) patients with severe hepatic-nephrotic disease, malignancy, infectious disease; 3) patients with cerebrovascular accident or peripheral vascular diseases; 4) pregnant and lactating women; 5) patients younger than 18 or older than 75; 6) patients who were unable to understand the study content or provide consent; and 7) patients who participate in other study programs in the meantime. For patients with ST-elevation myocardial infarction, they are usually included in the category of acute myocardial infarction because ST-elevation myocardial infarction is a specific type of acute myocardial infarction.

Study procedure

According to the treatment procedure, blood samples were taken for the measurement of cardiac biomarkers, including ischaemia-modified albumin, creatine kinase-MB and cardiac Troponin T. Meanwhile, ECG was done to identify the ischaemic changes. All these examinations were done in emergency department within 30 minutes, Blood samples were tested within 15 minutes. The demographics, including ageing, gender, hypertension, smoking, diabetes mellitus, and hyperlipidaemia were documented. The serum levels of cardiac biomarkers mentioned above and positive ECG findings were also recorded for further analysis. Serum ischaemia-modified albumin concentrations were measured by the albumin cobalt binding test described previously.[13] All serum levels were measured in our clinical laboratory.

Study definitions and final diagnosis

Positive ECG findings were defined as ST segment elevation or depression $\geq$0.1 mV, or T wave inversion $\geq$0.2 mV in at least two contiguous leads. ECGs showing no ST segment shifts or T wave changes were considered negative. As we aimed at new-onset ischaemia, pathological Q waves and left bundle branch block were considered to be negative. Definition of acute coronary syndrome included the diagnosis of UAP, non-ST-segment elevation myocardial infarction, and ST-elevation myocardial infarction. The diagnosis of ST-elevation myocardial infarction was defined according to World Health Organization definition of myocardial infarction (2008–09 revision) and the 2013 guideline of ACCF/AHA.[14,15] The criteria includes: persistent chest pain for more than 30 minutes, ST elevation on two or more adjacent leads on ECG

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and elevation of cardiac troponin T, and creatine kinase. The diagnosis of UAP and non-ST-segment elevation myocardial infarction was made with reference to the ACC/ESC guidelines for non-ST segment elevation acute coronary syndrome.[16,17] Patients with typical chest pain but without ST-segment elevation were diagnosed as non-ST segment elevation acute coronary syndrome. Typical chest pain was evaluated based on the Grading of angina pectoris by Canadian cardiovascular society. The working diagnosis of non-ST segment elevation acute coronary syndrome, based on the measurement of troponins, will be further qualified as non-ST-segment elevation myocardial infarction (positive cardiac troponin T) or UAP (negative cardiac troponin T). Coronary angiography was carried out to confirm the diagnosis of acute coronary syndrome. A stenosis ≥70% in any major coronary artery was defined to be positive in angiogram. Final diagnosis of acute coronary syndrome depended on clinical presentations, diagnostic tools, angiography, and risk factors. Patients with no positive evidences of acute coronary syndrome or with a confirmed non-cardiac disease caused their chest pain were diagnosed as non-ischaemic chest pain.

Statistical analysis

Results were expressed as mean ± standard deviation for continuous variables and frequencies for categorical variables. Differences between groups were examined by non-parametric test and chi-square test for continuous and categorical variables, respectively. An alpha value of 0.05, corresponding to a p value <0.05, served as criterion for establishing statistical significance. Analysis was performed using SPSS (Version 19.0) and STATA (Version 16.0).

Results

Baseline characteristics

A total of 200 patients (85 male, 115 female) in accordance with the inclusion criteria were included in the final study, and the mean age was 63.99 ± 9.85. Patients were divided into acute coronary syndrome group and non-ischaemic chest pain group after the diagnosis was made according to the guidelines. At last, 36 patients were included into the non-ischaemic chest pain group after the exclusion of acute coronary syndrome, and the rest 164 patients were in acute coronary syndrome group. As the results shown in Table 1, the demographics in two groups were not significantly different in most aspects, while patients in acute coronary syndrome group had obviously higher ratios of hypertension and previous CHD history ($p < 0.05$, $p < 0.01$). As an important factor of the positive detection of cardiac biomarkers, we recorded their onset time of chest pain. Patients with acute coronary syndrome came to emergency department after 2.91 ± 0.56 hours, while the came to emergency department average time was 3.14 ± 0.44 hours in non-ischaemic chest pain group. Though the difference in onset time was not statistically significant, patients of acute coronary syndrome came to emergency department earlier than non-ischaemic chest pain patients, which was against the positive detection of cardiac biomarkers. Timely ECG was done for the observation of cardiac ischaemia. According to the definition of positive ECG changes, almost all the patients in acute coronary syndrome group showed ischaemic ST-segment changes in ECGs, while few positive results were found in non-ischaemic chest pain group ($p < 0.001$). Cardiac biomarkers were measured in emergency department within 30 minutes. Results showed that the serum levels of cardiac troponin T and creatine kinase-MB were significantly higher in acute coronary syndrome group (both $p < 0.001$). Similarly, patients in acute coronary syndrome group had higher levels of ischaemia-modified albumin (0.54 ± 0.23 Absorbance Units (ABSU)) than those in non-ischaemic chest pain group (0.31 ± 0.11 ABSU, $p < 0.001$). We did receiver operating characteristic curve (ROC) analysis for the significance of ischaemia-modified albumin in acute coronary syndrome. The area under the curve of ischaemia-modified albumin was 0.951 (95% CI: 0.914–0.988, $p = 0.000$), and the optimum cut-off level was 0.415 ABSU (sensitivity = 82.3% and specificity = 94.4%). Then, according to the cut-off level, we defined serum level>0.415 ABSU as positive results. In patients with acute coronary syndrome, the positive rate of ischaemia-modified albumin was 91.5% (150/164), while the rate of cardiac troponin T was 82.3% (135/164). According to the onset time, we collected acute coronary syndrome patients to analyse the significance of early detection. Results showed that in patients who came to emergency department within 2 hours after onset, the positive rate of ischaemia-modified albumin was 84.8% (78/92), while the positive rate of cardiac troponin T was 60.9% (56/92). When we combined cardiac biomarkers with ECG changes, the results showed ischaemia-modified albumin was superior to cardiac troponin T (94.5% vs. 90.2%). When we focused on the biomarkers' serum level in UAP patients, the advantage of ischaemia-modified albumin was more obvious. The serum level of ischaemia-modified albumin in UAP patients was significantly higher than that in non-ischaemic chest pain patients, while the serum level of cardiac troponin were close in UAP and non-ischaemic chest pain patients. Moreover, the positive rate of ischaemia-modified albumin was obviously higher than cardiac troponin in UAP patients. These results demonstrated the favourable sensitivity and specificity of ischaemia-modified albumin in the early diagnosis of acute coronary syndrome, especially in UAP.

The effect of hypertension in ischaemia-modified albumin of acute coronary syndrome patients

To evaluate hypertension's effect on the serum level of ischaemia-modified albumin in patients with acute coronary syndrome, further grouping was done based on the complication of hypertension. As shown in Table 1, 100 acute coronary syndrome patients had a history of hypertension, while the other 64 did not. Again, demographic analysis was done to evaluate the feasibility of further study. Results in Table 2 display no significantly statistical differences in age, the ratio of complications, and other baseline characteristics. However, acute coronary syndrome patients with hypertension came to emergency department earlier than patients without hypertension ($p < 0.05$), which might prompt a better consciousness of disease in patients with hyperntension. As the severity of acute coronary syndrome may have effect on the serum level of cardiac biomarkers, we recorded the different types of acute coronary syndrome in two groups. Results showed that the proportions of acute coronary syndrome in two groups were similar and the differences were not significant. At last, we analysed the serum level of these biomarkers. Patients with hypertension had relatively higher serum levels of cardiac troponin T and ischaemia-modified albumin. However, only the

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Table 1. Baseline characteristics

Characteristic	ACS (n = 164)	NICP (n = 36)	p-value
Age (years)	64.63 ± 9.43	63.18 ± 10.96	0.209
Female (%, n)	55.5(91)	66.7(24)	0.315
BMI (kg/m^2)	23.17 ± 2.49	22.32 ± 2.96	0.074
Hypertension (%, n)	60.9(100)	27.8(10)	0.023*
Diabetes mellitus (%, n)	31.7(52)	25.0(9)	0.354
Tobacco use (%, n)	24.4(40)	25.0(9)	0.548
Hyperlipidaemia (%, n)	17.7(29)	13.9(5)	0.426
Previous CHD (%, n)	73.8(121)	27.8(10)	0.005**
Onset time (h)	2.91 ± 0.56	3.14 ± 0.44	0.025*
Cardiac biomarkers			
cTnT (ng/mL)	0.112 ± 0.091	0.009 ± 0.015	<0.001***
CK-MB (ng/mL)	4.56 ± 1.88	1.69 ± 1.54	<0.001***
IMA (ABSU)	0.54 ± 0.23	0.31 ± 0.11	<0.001***
ECG changes (%, n)	90.2 (148)	16.7 (6)	<0.001***

*p < 0.05; **p < 0.01; ***p < 0.001.
Abbreviations: BMI: body mass index; cTnT: cardiac troponin T; CK-MB: creatine kinase-MB; IMA: ischaemia-modified albumin; ECG: electrocardiogram.

Table 2. IMA in ACS combined with HBP

Characteristic	ACS-HBP (n = 100)	ACS-non-HBP (n = 64)	p-value
Age (years)	63.93 ± 10.01	63.68 ± 9.65	0.437
Female (%, n)	63.0(63)	51.9(28)	0.119
BMI (kg/m^2)	23.17 ± 1.88	22.72 ± 2.04	0.075
Diabetes mellitus (%, n)	31.0(31)	32.8(21)	0.493
Tobacco use (%, n)	28.0(28)	18.8(12)	0.191
Hyperlipidaemia (%, n)	22.0(22)	17.2(11)	0.341
Previous CHD (%, n)	85.0(85)	56.3(36)	0.067
On-set time (h)	2.86 ± 0.45	3.04 ± 0.73	0.026*
ACS distribution			
STEMI (%, n)	45.0(45)	37.5(20)	0.324
NSTEMI (%, n)	33.0(33)	34.4(22)	0.510
UAP (%, n)	22.0(22)	28.1(18)	0.303
Cardiac biomarkers			
cTnT (ng/mL)	0.118 ± 0.078	0.109 ± 0.044	0.201
CK-MB (ng/mL)	3.96 ± 1.59	4.41 ± 2.09	0.060
IMA (ABSU)	0.60 ± 0.39	0.48 ± 0.31	0.008**

*p < 0.05; **p < 0.01; ***p < 0.001.
Abbreviations: BMI: body mass index; CHD: coronary heart disease; ACS: acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; cTnT: cardiac troponin T; CK-MB: creatine kinase-MB; IMA: ischaemia-modified albumin; ECG: electrocardiogram.

difference of ischaemia-modified albumin was statistically significant (p = 0.008), which might reveal the effect of hypertension in serum level of ischaemia-modified albumin in acute coronary syndrome patients in a certain degree. The multivariate Cox regression analysis showed a significant association between hypertension and ischaemia-modified albumin after adjusting for other relevant factors, including DM, smoking, onset time, and others (p = 0.041).

Discussion

Results above have shown that ischaemia-modified albumin is effective for the early diagnosis of acute coronary syndrome in patients presenting with chest pain. The abnormal increase of ischaemia-modified albumin occurs earlier than cardiac troponin T in patients with acute coronary syndrome. In addition, the positive rate of ischaemia-modified albumin is also higher than

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cardiac troponin T. Early detection of ischaemia-modified albumin combined with electrocardiographic examinations is more sensitive in the diagnosis of acute coronary syndrome in patients with continuous chest pain

The early diagnosis of acute coronary syndrome is in bad need because of the severity of acute coronary syndrome. Traditional cardiac biomarkers in clinic are not specific and sensitive enough. They often show a greater rise approximately 3–6 h after the onset of the myocardial cell injury, or necrosis, which limits their early diagnostic significance. In the progress of acute coronary syndrome, coronary stenosis, and therosclerotic plaque lead to myocardial ischaemia. Therosclerotic rupture or acute thrombotic events cause myocardial necrosis. Thus, a biochemical marker of ischaemia is potentially valuable in theory. It may improve our ability to risk stratifying acute chest pain patients and guide therapeutic decisions in the earlier stage. Different from cardiac troponin, positive detection of ischaemia-modified albumin does not mean myocardial necrosis, but reflects the myocardial ischaemia. This reflection behaves as a capacity of plasma albumin to bind to heavy metal ions such as cobalt, which is the foundation of ischaemia-modified albumin's detection. The increase of ischaemia-modified albumin is reported to be positive within minutes of ischaemia, allowing detection before the incidence of myocardial necrosis.[18] Over the past few years, several researches aimed on the significance of ischaemia-modified albumin in acute coronary syndrome have been done. Sinha et al showed that compared with ECG and cardiac troponin T or cTnI, ischaemia-modified albumin was significantly sensitive in the diagnosis of acute ischaemic chest pain.[19] Roy D and his colleagues reported the diagnostic significance of ischaemia-modified albumin in patients with acute chest pain but normal or non-diagnostic 12-lead ECGs and negative cardiac troponin T.[20] In addition, a meta-analysis of ischaemia-modified albumin affirmed the value of ischaemia-modified albumin in diagnosing acute coronary syndrome.[18] The findings of our study confirmed the positive results of previous researches, not only the reliable value in diagnosis of acute coronary syndrome but also priority over cardiac troponin T. Moreover, we demonstrated the great diagnostic value of ischaemia-modified albumin in patients with UAP, which is difficult for cardiac troponin T.

However, few studies focused on the different levels of ischaemia-modified albumin in patients with hypertension, especially patients with acute coronary syndrome combined with hypertension. As is known to all, the incidence of target organ damage caused by hypertension is associated with the progress and severity of hypertension. Target organ damage often occurs in heart, kidney and brain, performing as chronic ischaemia, which is the base of ischaemia-modified albumin. We studied the different levels of ischaemia-modified albumin in patients with different stages of hypertension. Results showed that the serum level of ischaemia-modified albumin is associated with their onset time, systolic blood pressure and diastolic blood pressure levels. The level of ischaemia-modified albumin in patients with hypertension is higher than that in patients without hypertension. Because of the positive results in the previous study, we analyzed the difference on ischaemia-modified albumin levels between acute coronary syndrome patients with or without hypertension. As expected, acute coronary syndrome patients with hypertension had a higher level of ischaemia-modified albumin. This result may contribute to the diagnosis of hypertension patients complained with acute chest pain.

Several limitations should not be ignored. First, the size of each subgroup is relatively small for the study on acute coronary syndrome combined with hypertension. Thus, additional researches should be done in a larger population to verify our results. Then, our study included patients with acute chest pain, but excluded healthy population. Therefore, we could not analyse the distribution of ischaemia-modified albumin in healthy population and compare the difference between them. Another limitation is that the detection of ischaemia-modified albumin was done by the albumin cobalt binding test, the unit of measurement was ABSU, which limited the comparison with other studies. At last, we measured the serum level of chosen biomarkers only once. Therefore, we could not observe the dynamic change of ischaemia-modified albumin and cardiac troponin T, so that it limited the comparison about sensitivity and specificity between them at different time points.

In conclusion, this study revealed the concentration change of ischaemia-modified albumin in patients with acute coronary syndrome and made contribution to the use of ischaemia-modified albumin in early diagnosis of acute coronary syndrome, especially in patients with hypertension. However, further studies should be done in the future to optimise the clinical applicability and accuracy.

Conclusions

In patients complained with acute chest pain, the serum measurement of ischaemia-modified albumin is potential valuable for the early diagnosis of acute coronary syndrome, especially combined with ECG. The serum level of ischaemia-modified albumin in acute coronary syndrome patients is significantly associated with hypertension.

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Competing interests. None.

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