Correlation Between Ischaemia Modified Albumin Level And Coronary Collateral Circulation

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DOI: 10.21203/rs.2.12560/v1

SUBJECT AREAS Cardiac & Cardiovascular Systems

KEYWORDS Coronary artery disease; Chronic total occlusion; Collateral circulation; Ischaemia modified albumin
Abstract

Objective

To investigate the correlation between ischemic modified albumin (IMA) level and coronary collateral circulation (CCC) in patients with chronic total occlusive disease (CTO).

Methods

Coronary angiography was performed in the Department of Cardiology, Zhongnan Hospital of Wuhan University from 2017-08 to 2019-02 to determine 128 patients with CTO lesions in at least one major coronary artery. According to the Rentrop evaluation criteria, the degree of CCC formation was divided into CCC poor formation group (Rentrop0-1 grade, n=69) and CCC formation good group (Rentrop2-3 grade, n=59). The IMA level of the patients was measured using an albumin-cobalt binding assay. Record and analyze the patient's general data, blood routine, total bilirubin (TBIL), blood lipids, uric acid (UA), left ventricular ejection fraction (LVEF) and other indicators, while recording the patient's occlusion of blood vessels.

Results

The proportion of platelet count and diabetes in the poor CCC group was higher than that in the good group (P<0.05). The ratio of ischemic modified albumin and total bilirubin in the poor CCC group was lower than that in the good group (P<0.05). Multivariate logistic regression analysis showed that ischemic modified albumin was positively correlated with CCC formation (OR=1.190, 95% CI (1.092-1.297), P<0.001), diabetes was negatively correlated with CCC formation (OR=0.285, 95% CI (0.094-0.864), P<0.05). Ischemic modified albumin predicts good formation of CCC under the ROC curve and the area under the ROC curve is 0.769.
(95% CI 0.686-0.851, P<0.001); the optimal cut-off value was 63.35KU/L, the sensitivity is 71.2%, specificity is 71%.

Conclusion

The IMA level is closely related to the good formation of CCC. The higher IMA level can be used as an effective predictor of the good CCC formation in CTO.

Background

Chronic total occlusion (CTO) is defined as the presence of TIMI 0 flow within an occluded arterial segment of greater than 3 months standing\cite{1}. Coronary collateral circulation (CCC) is a small blood flow channel between different coronary arteries or different segments of the same coronary artery. Usually, these collateral blood flows are extremely small under physiological conditions and are not involved in the blood circulation of the coronary arteries. Under the stimulation of chronic or repeated myocardial ischemia, the collateral vessels gradually open up and develop into functional collateral circulation\cite{2}. Well-developed CCC has the function of protecting ischemic myocardium, can increase coronary blood flow reserve, help protect left ventricular function, and mitigate myocardial infarcts and improve survival\cite{3-4}.

Ischaemia-modified albumin (IMA) is a change in the N-terminal sequence of albumin amino group in human serum albumin (HSA) during tissue ischemia, resulting in a decrease in the ability to bind to free metal ions such as cobalt, copper and nickel\cite{5}. IMA is currently considered a new biomarker for myocardial ischemia, which can be elevated in the early stages of irreversible necrosis of cardiomyocytes. Compared with other myocardial injury biochemicals in patients
with acute coronary syndrome Markers can be detected earlier and with higher
sensitivity\textsuperscript{[6-7]}.

Current studies have shown that IMA can sensitively reflect early myocardial
ischemia, but the relationship between IMA levels and CCC in CTO is uncertain. This
study aimed to explore the correlation between IMA level and CCC.

Methods

\textbf{Univariate analysis:} The proportion of platelet count and diabetes in poor CCC
group was higher than that in good group (P<0.05); the levels of IMA and total
bilirubin in the poor CCC group was lower than that in the good group
(P<0.05). There was no significant difference in other indicators between the two
groups (P>0.05)(Table 1).

\textbf{Multivariate Logistic regression analysis:} With the formation of CCC as
dependent variable and the factors P < 0.1 in the univariate analysis as
independent variable, multivariate logistic regression analysis showed that diabetes
was negatively correlated with CCC [OR=0.285 95% CI(0.094-0.864) P<0.05]; IMA
was positively correlated with CCC [OR=1.190 95% CI(1.092-1.297) P<0.001]. The
results showed that the level of IMA and diabetes were independent factors
affecting CCC(Table 2).

\textbf{Rentrop grading correlation analysis:} The level of IMA at Rentrop\textsubscript{0}(58.79±5.00)
was lower than that at Rentrop\textsubscript{1}(64.44±4.36), Rentrop\textsubscript{2}(65.50±5.93) and Rentrop\textsubscript{3}
(67.79±5.79), P <0.001. There was no significant difference in the level of IMA
between Rentrop\textsubscript{1} and Rentrop\textsubscript{2} and Rentrop\textsubscript{3} levels (P>0.05). There was no
significant difference between the level of IMA at Rentrop\textsubscript{2} and Rentrop\textsubscript{3} (P >0.05)
(Figure 1).
**ROC curve results:** The area under curve was 0.769 (95% CI: 0.686-0.851, P<0.001). The optimal cut-off point was 63.35 KU/L, with a sensitivity of 71.2% and a specificity of 71% (Figure 2).

**Discussion**

This study shows that high IMA level is an independent predictor of CCC and positively correlated with CCC formation. In addition, this study found a negative correlation between diabetes and CCC formation.

The formation of coronary collateral vessels is a complex process. When the blood flow of the coronary artery is severely reduced or occluded, the anastomotic branches with a diameter of 20-350 μm between the coronary arteries gradually form functional collateral circulation through a series of mechanisms under the action of end-to-side pressure of the coronary artery\(^2\). When coronary artery stenosis or occlusion is severe, good CCC can improve myocardial ischemia, protect myocardial contraction function, improve clinical symptoms, reduce the incidence of myocardial infarction, reduce the size of myocardial infarction, thereby reducing the mortality of ischemic events and improving prognosis\(^3,4,10\). However, the determinants and influencing factors of CCC formation are also complex. The degree of CCC formation may be different with the same degree of coronary stenosis or occlusion. Studies have shown that the formation of CCC is positively correlated with the severity of coronary artery stenosis, multiple severe stenosis and duration of lesion\(^11\). Meanwhile, a large number of studies have shown that the formation of CCC is also closely related to hypertension, diabetes, metabolic syndrome, oxidative stress, endothelial dysfunction, endogenous mediators and vascular
Inflammation\textsuperscript{[12-14]}. Ischemia modified albumin is considered as a new biomarker for the assessment of myocardial ischemia, which has early diagnostic value for myocardial ischemia\textsuperscript{[7]}. The formation of IMA is mainly related to the oxidative stress response caused by ischemia reperfusion injury and other cardiac and extracardiac events. IMA is the product formed by the oxidation of albumin, and the higher the oxidation stress, the higher the IMA level\textsuperscript{[15-16]}. It is also closely related to the amount of oxygen free radicals formed during ischemia \textsuperscript{[17]}. The production of IMA is also related to factors other than cardiac factors, including blood vessels, brain and skeletal muscle\textsuperscript{[5]}. Previous studies have found that oxidative stress is closely related to the formation of CCC. Reactive oxygen species (ROS) play an important role in endothelial cell migration, angiogenesis and cell proliferation, further affecting the formation of CCC\textsuperscript{[18]}. Demirbag et al.\textsuperscript{[19]} found that oxidative stress was positively correlated with the good CCC in CTO. Gök et al.\textsuperscript{[20]} showed that high IMA level is closely related to the good formation of CCC, which can be used as a simple and effective predictor of good CCC.

Diabetes mellitus is an important risk factor for cardiovascular disease. Studies have found that diabetes has adverse effects on coronary collateral artery formation and angiogenesis through a variety of mechanisms. Diabetic patients have more severe, diffuse and complex coronary atherosclerosis, which can lead to the decrease of coronary collateral artery pressure, which is not conducive to collateral formation. When diabetes mellitus occurs, the parameters of vascular growth factor change, endothelial dysfunction reduces the production of nitric oxide, which has a negative impact on the formation of neovascular intima and
angiogenesis. Inflammatory cells such as neutrophils, monocytes and macrophages also play a negative role in CCC\textsuperscript{[21]}. The results of this study are consistent with previous research conclusions.

At present, little research has been done on the relationship between ischaemia modified albumin and coronary collateral circulation. The results of this study show that higher IMA level is positively correlated with the good CCC, which is consistent with previous research conclusions. It is believed that CCC is easier to form when oxidative stress increases, and that the increase of oxidative stress can lead to a higher level of IMA. However, there are still some shortcomings in this study: this study is a retrospective study; the sample size is small; no follow-up of the outcome; there are many factors influencing the formation of CCC, and a comprehensive multi-factor analysis is not available.

Conclusions

The results of this study showed that higher IMA level was positively correlated with the good CCC, suggesting that IMA level was closely related to the good CCC, and that higher IMA level could be an effective predictor of the good CCC in patients with CTO. Of course, more large-scale studies are needed to explore the relationship between ischemic modified albumin and coronary collateral circulation.

Abbreviations

IMA: ischemic modified albumin; CCC: coronary collateral circulation; CTO: chronic total occlusive disease; TBIL: total bilirubin; LVEF: left ventricular ejection fraction; TIMI: Thrombolysis in myocardial infarction; LAD: left anterior
Acknowledgements

None.

Authors’ contributions

XC and ZQW: study design; XC, YL and LHT: data collection, data analysis; XC and YL: design and statistical analysis and preparing the manuscript. All authors took part in rewriting and approval of the final manuscript. ZQW is responsible for the integrity of the work as a whole.

Funding

No funding.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Zhongnan Hospital of Wuhan University reviewed and approved the study. All patients gave written informed consent to take part in this study. The study was conducted in accordance with 1964 Helsinki Declaration.

Competing interests

The authors declare that they have no competing interests.

Consent for publication
Not applicable.

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Tables

| Variables                      | Good CCC (n=59) | Poor CCC (n=69) | P    |
|-------------------------------|----------------|----------------|------|
| Age(years)                    | 60.92±11.61    | 61.28±11.61    | 0.861|
| Male                          | 45(76.3)       | 45(65.2)       | 0.172|
| Coronary heart disease        | 10(16.9)       | 5(7.2)         | 0.089|
| Hypertension                  | 39(66.1)       | 35(50.7)       | 0.079|
| Diabetes mellitus             | 9(15.3)        | 24(34.8)       | 0.012|
| Smoking                       | 25(42.4)       | 27(39.1)       | 0.710|
| Drinking                      | 10(16.9)       | 14(20.3)       | 0.629|
| Statins                       | 8(13.6)        | 3(4.3)         | 0.064|
|                                | Aspirin | ACEI/ARB |  p    |
|--------------------------------|---------|----------|-------|
| Platelet (×10^9/L)             | 195.97±55.46 | 218.30±71.62 | 0.049 |
| Neutrophil (×10^9/L)           | 5.45(3.70,6.21) | 6.48(3.75,8.78) | 0.091 |
| Lymphocyte (×10^9/L)           | 1.64(1.12,1.89) | 1.41(1.02,1.79) | 0.105 |
| Monocyte (×10^9/L)             | 0.66(0.37,0.64) | 0.56(0.36,0.63) | 0.636 |
| Total cholesterol (mmol/L)     | 4.79(3.72,5.30) | 4.43(3.58,5.21) | 0.247 |
| Triglyceride (mmol/L)          | 2.14(1.06,2.19) | 1.81(0.99,2.22) | 0.602 |
| HDL-C (mmol/L)                 | 0.98(0.82,1.11) | 1.88(0.78,1.10) | 0.482 |
| LDL-C (mmol/L)                 | 2.94±1.06     | 2.80±0.89     | 0.418 |
| LP(a) (mg/L)                   | 214.96(76.30,289.10) | 202.16(56.85,244.45) | 0.324 |
| Total bilirubin (μmol/L)       | 15.04±5.63    | 12.58±5.01    | 0.010 |
| IMA (KU/L)                     | 66.31±5.94    | 60.51±5.45    | <0.001 |
| Uric acid (μmol/L)             | 373.61±111.65 | 368.76±108.56 | 0.804 |
| LVEF (%)                       | 60.67±10.28   | 62.34±8.96    | 0.327 |
| Occlusive vessels              |          |           |       |
| Multivessel                    | 13(22.0)     | 8(11.6)     | 0.112 |
| LAD                            | 25(42.4)     | 23(33.3)    | 0.292 |
| LCX                            | 4(6.8)       | 12(17.4)    | 0.070 |
| RCA                            | 17(28.2)     | 26(37.7)    | 0.290 |

CCC: coronary collateral circulation; ACEI: angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor antagonist; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; LP(a): lipoprotein a; IMA: ischemic modified albumin; LVEF: left ventricular ejection fraction; Occlusive vessels: more than two main coronary arteries; LAD: left anterior descending artery; LCX: left circumflex; RCA: Right coronary artery

**Figures**
Figure 1

Comparison of IMA in various Rentrop grades (comparison with Rentrop 0, aP < 0.001; bP < 0.05).
IMA predicts the ROC curve of CCC: AUC: 0.769 (95% CI: 0.686-0.851, P<0.001), cut-off point: 63.35 KU/L, 71.2% sensitivity, 71% specificity.