Predictive value of combining the level of lipoprotein-associated phospholipase A2 and antithrombin III for acute coronary syndrome risk

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Received August 29, 2018; Accepted October 16, 2018

DOI: 10.3892/br.2018.1162

Abstract. The aim of the present study was to observe the role of lipoprotein-associated phospholipase A2 (Lp-PLA2) and antithrombin III (AT-III) in patients with acute coronary syndrome (ACS), and the combination of Global Registry of Acute Coronary Events (GRACE) score to determine the value of coronary heart disease risk stratification. A total of 309 patients admitted to the Affiliated Hospital of Xuzhou Medical University were enrolled. The patients were divided into two groups: The ACS (183 cases) and control (126 cases) groups. Blood levels of Lp-PLA2 and AT-III were measured. Based on GRACE score, the patients with ACS were divided into three subgroups: Low risk (GRACE score ≤108), middle risk (GRACE score 109-140) and high risk (GRACE score >140). The levels of Lp-PLA2 and AT-III were compared among different groups, and based on Gensini score, patients with ACS were divided into four groups by quartiles. Lp-PLA2 levels in the ACS group were significantly increased compared with the control group (P<0.05), but the AT-III levels were decreased compared with the control group (P<0.05). In the ACS group, Lp-PLA2 levels increased sequentially from the low risk to high risk subgroups (all P<0.05); compared with the low risk and middle risk subgroups, the AT-III activity levels were decreased in the high risk subgroup, and the Gensini scores were increased (all P<0.05). In the ACS group, with the increase of Gensini scores, the levels of Lp-PLA2 and AT-III exhibited increasing and decreasing trends, respectively (P<0.05). The logistic regression model demonstrated that Lp-PLA2 [odds ratio (OR) =1.077; P<0.001]; and GRACE score (OR=1.026; P=0.028) were risk factors, while AT-III was a protective factor (OR=0.958; P=0.012) for ACS. Correlation analysis indicated a positive association of Lp-PLA2 level with Gensini scores (r=0.52; P<0.01) and GRACE score (r=0.48; P<0.01), and a negative association between AT-III level and Gensini scores (r=-0.25; P<0.01) and GRACE scores (r=-0.34; P<0.01). The levels of Lp-PLA2 and AT-III exhibited predictive values in patients with ACS, and are associated with the severity of coronary artery stenosis.

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Abbreviations: Lp-PLA2, lipoprotein-associated phospholipase A2; AT-III, antithrombin III; GRACE, Global Registry of Acute Coronary Events score; CAG, coronary artery angiography

Key words: acute coronary syndrome, lipoprotein-associated phospholipase A2, antithrombin III, GRACE score

Introduction

Cardiovascular disease is the leading cause of mortality worldwide (1). The major pathogenic mechanisms are atherosclerosis (AS) and thrombosis (2). At present, the mechanism of AS has not been specified. Increasing evidence has suggested the role of the chronic inflammatory response to AS, the oxidative stress response to its significant characteristics and the formation of atherosclerotic plaques is the pathophysiological basis of coronary heart disease (3). Subsequently, the rupture of the coronary atherosclerotic plaques and disruption of the coagulation-anticoagulation system are responsible for acute coronary artery events. Previously, studies have confirmed lipoprotein-associated phospholipase A2 (Lp-PLA2) as a novel type of inflammatory marker in coronary heart disease (4,5), and it is derived from the secretion of macrophages in the atherosclerotic plaques, which may promote the transformation of macrophages into foam cells and promote the instability of plaques. The increase of Lp-PLA2 indicates that the risk of plaque rupture is increased (6-8). In addition, the high level of antithrombin III (AT-III) may lead to hypercoagulability, and promote thrombosis (9). In the present study, levels of plasma Lp-PLA2, changes in AT-III activity level, and joint Global Registry of Acute Coronary Events (GRACE) scores were measured in patients with acute coronary syndrome (ACS) to assess the values of these parameters in ACS risk stratification, and analysis of their associations with the severity of coronary artery lesions performed.

Patients and methods

Patients populations. From February 2016 to February 2017, 309 patients were admitted to the Affiliated Hospital of Xuzhou

Medical University (Xuzhou, China), including 152 females and 157 males, with an average age of 62±7.6 years. All the selected patients underwent coronary angiography, and according to the results were divided into an ACS group (183 cases) and control group (126 cases). ACS was defined as at least one from the left main coronary artery, left anterior descending artery, left circumflex artery or right coronary artery exhibiting a stenosis of >50%. Control cases were defined as those with coronary artery stenosis of <50% and normal blood flow. The study protocol was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University. All patients provided written informed consent for the procedure.

Exclusion criteria. There were several exclusion criteria used: i) Severe liver and renal dysfunction; ii) thrombotic diseases, including pulmonary embolism and lower extremity venous thrombosis; iii) patients with malignant arrhythmia without treatment; iv) patients with thyroid or adrenal dysfunction; v) patients with acute and chronic infectious diseases, high fever and malignant tumor; and vi) patients with a history of myocardial infarction, PCI or CABG.

Data collection. General data from the selected patients: Age; sex; smoking history; past clinical history, including hypertension, diabetes, myocardial infarction, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); and a record of blood pressure, heart rate, cardiac arrest and left ventricular ejection fraction on admission was collected. Concomitantly, fasting venous blood samples, Lp-PLA2 levels, AT-III activity levels, liver and kidney function, blood glucose, blood lipids and other indicators were measured within 24 h after admission. The above indexes were measured by the laboratory of the Affiliated Hospital of Xuzhou Medical University; the Lp-PLA2 kit was provided by Nanjing Norman Biological Technology Co., Ltd. (Nanjing, China; cat. no. 20162400274) and the Berichrom Antithrombin III kit was provided by Siemens Healthcare Diagnostics Products GmbH (Marburg, Germany; cat. no. 20152401859), which were used according to the manufacturer's protocols.

GRACE score. This scoring system includes age, heart rate, systolic blood pressure, Killip heart function classification, ECG ST segment change, incidence of cardiac arrest, myocardial enzyme spectrum and serum creatinine levels (10). Based on the GRACE score, patients with ACS were divided into three subgroups: The low risk subgroup (score ≤108; n=75), middle risk subgroup (score 109-140; n=60), and high risk subgroup (score >140; n=48).

Gensini score. The Gensini severity score, a measure of the severity of coronary stenosis, was also calculated; a severity coefficient was calculated for each segment (0, 1, 2, 4, 8, 16, or 32 according to the degree of stenosis) and the importance of the segment was rated (5 for the left main trunk to 0.5 for the most distal segments) (11). Using the Gensini scale, the coronary lesions were measured in all the patients who were in the ACS group. Based on the results, the ACS group was divided into four groups by quartiles: Group 1 (n=45); group 2 (n=44); group 3 (n=46); and group 4 (n=48).

Coronary angiography. Coronary angiograms were used to take a radial artery or femoral artery angiogram. The results were evaluated by two experts.

Statistical analysis. All continuous variables in the study were normally distributed. Continuous variables were presented as the mean with standard deviation and compared using one-way analysis of variance. Categorical variables were compared using the χ^2 test. Logistic regression was used to evaluate the association between Lp-PLA2, AT-III and GRACE score by calculating odds ratios (ORs) or adjusted ORs with 95% confidence intervals (CIs). Pearson correlation for normal variables or Spearman's correlation for skewed variables was used to evaluate the associations between study parameters. All statistical tests were two-sided, and the significance level was set as P<0.05. The statistical analyses were performed using SPSS software, version 19.0 (IBM Corporation, Armonk, NY, USA).

Results

Baseline data. The clinical characteristics are presented in Table I. When compared with the control group, the patients in the ACS group were older (P<0.001), with increased proportions of hypertension and diabetes (all P<0.05). The ACS group exhibited high levels of HDL-C and AT-III activity, and low levels of Lp-PLA2 (all P<0.05). There was no significant difference in body mass index, systolic blood pressure and serum creatinine in the two groups.

The comparison of Lp-PLA2, AT-III and Gensini scores between the GRACE-graded risk stratification groups was then performed. In the ACS group, Lp-PLA2 levels increased sequentially from low risk, to middle risk to high risk subgroups (all P<0.05); compared with the low risk and middle risk subgroups, the high risk subgroup exhibited decreased AT-III activity and increased Gensini scores (both P<0.05); while AT-III activity and Gensini scores was similar between low risk and middle risk subgroups (P>0.05; Table II).

Lp-PLA2 levels, AT-III activity and general data in each of the Gensini scores quartiles were compared, and the general data including sex, age, body mass index, fasting blood glucose, blood lipids, blood creatinine and combined hypertension and diabetes were not statistically significant (P>0.05). The level of Lp-PLA2 were increased with increases in Gensini score, and there were statistically significant differences between the 1st, 2nd and 3rd subgroups groups; however, when comparing the 3rd and 4th quartile subgroups, while the level of Lp-PLA2 was increased the difference was not statistically significant (P>0.05). The level of AT-III was decreased with increases in Gensini score. The difference was statistically significant between the 4th and 1st subgroups (P<0.05), while there were no significant differences between the 1st, 2nd and 3rd subgroups (P>0.05). The results are presented in Table III.

Logistic regression analysis for risk factors for coronary heart disease. The logistic regression model included ACS as the dependent variable, Lp-PLA2, AT-III and GRACE scores as independent variables and the associated risk factors of age, sex and total cholesterol levels as fixed variables. The result indicated that the level of Lp-PLA2 [odds ratio (OR) =1.077;

Table I. Baseline clinical characteristics of the control and ACS groups.

Characteristics	Control group (n=126)	ACS group (n=183)	P-value
Age, years	58.2±8.4	65.3±9.2	<0.001
Male, n (%)	49 (38.9)	108 (59.0)	<0.001
Body mass index, kg/m^2	21.5±4.8	22.8±5.2	0.248
Hypertension, n (%)	55 (43.7)	140 (76.5)	<0.001
Diabetes, n (%)	25 (19.8)	62 (33.9)	<0.001
Systolic pressure, mmHg	132.6±24.3	134.5±22.8	0.376
Serum creatinine, μmol/l	62.1±11.8	64.5±10.6	0.332
Triglyceride, mmol/l	1.62±0.70	1.85±1.28	0.010
Total cholesterol, mmol/l	5.11±1.17	4.76±1.34	0.397
High-density lipoprotein, mmol/l	1.42±0.36	1.26±0.43	<0.001
Low-density lipoprotein, mmol/l	2.35±0.81	2.40±0.76	0.776
Lipoprotein-associated phospholipase, ng/ml	134.6±30.0	346.3±92.1	<0.001
Antithrombin III, %	98.6±10.8	91.6±12.4	<0.001

ACS, acute coronary syndrome.

Table II. Comparison of Lp-PLA2, AT-III and Gensini scores in the GRACE graded risk stratification groups.

	GRACE stratification groups		
Parameters	Low risk (n=75)	Middle risk (n=60)	High risk (n=48)
Lp-PLA2, ng/ml	253.60±89.72	389.26±122.50[a]	436.58±96.46[a]
AT-III, %	95.62±11.38	90.33±10.27	86.57±12.86[a]
Gensini score	22.76±19.20	41.52±21.71	60.02±33.46[a]

[a]P<0.05 vs. low risk group. Lp-PLA2, lipoprotein-associated phospholipase; AT-III, antithrombin III; GRACE, Global Registry of Acute Coronary Events.

P<0.001) and GRACE score (OR=1.026; P=0.028) were risk factors, while AT-III was a protective factor (OR=0.958; P=0.012) for ACS (Table IV).

Correlation analysis. Correlation analysis indicated a positive association between Lp-PLA2 level with Gensini scores (r=0.52; P<0.01) and GRACE scores (r=0.48; P<0.01), and a negative association between AT-III activity levels with Gensini scores (r=-0.25; P<0.01) and GRACE scores (r=-0.34; P<0.01).

Discussion

The occurrence of acute coronary events is primarily due to the rupture of unstable plaques, where dysregulated blood lipids are involved in the formation of atherosclerotic plaques and the subsequent inflammatory response often causes the plaque to be unstable or even rupture. Plaque rupture releases tissue factor and platelet activating factor, which causes platelets to accumulate rapidly and promotes the release of a large number of inflammatory factors, increasing the expression of coagulants and thereby aggravating thrombosis.

Lp-PLA2 is a member of the phospholipase A2 superfamily, and is also known as platelet-activating factor acetylhydrolase (12). It is primarily produced by monocytes and macrophages. Lp-PLA2 is able to hydrolyze oxidative phospholipids in oxidized low-density lipoprotein (ox-LDL) (13). Following LDL oxidation, 2 types of proinflammatory factors are produced: lyso-phosphatidylcholine and oxidized fatty acids. These factors damage vascular endothelial function, and the mononuclear cells are aggregated into the vascular intima and transformed into macrophages, which eventually phagocytose ox-LDL to form foam cells, leading to the formation of atherosclerotic plaques (14). In addition, lyso-phosphatidylcholine and oxidized fatty acids may feedback to stimulate macrophages to produce more Lp-PLA2. This cycle accelerates the progression of AS, promotes plaque instability and increases the risk of cardiovascular events (15-19). In 2012, the American and European guidelines recommended the incorporation of Lp-PLA2 measurements into patient cardiovascular risk assessment protocol (20,21). Although increased Lp-PLA2 levels have been indicated to be associated with an increased cardiovascular risk, the specific clinical effect of Lp-PLA2 levels remains unclear. Therefore, additional studies are required to establish the causal role of Lp-PLA2 in cardiovascular events. The West of Scotland Coronary Prevention Study was the first study demonstrating an association between

Table III. Comparison of Lp-PLA2 levels and AT-III activity levels in the Gensini scores quartiles.

	Gensini score quartiles			
Parameters	1st (n=45)	2nd (n=44)	3rd (n=46)	4th (n=48)
Lp-PLA2, ng/ml	257.2±77.5	336.8±76.8[a]	385.4±78.1[a]	391.2±65.2[a]
AT-III, %	94.6±11.2	92.3±11.5	89.5±13.2	86.8±12.4[a]

[a]P<0.05 vs. 1st quartile. Lp-PLA2, lipoprotein-associated phospholipase; AT-III, antithrombin III.

Table IV. Logistic regression model of risk factors for acute coronary syndrome.

Variables	Partial regression coefficients	Standard error	Wald value	Odds ratio (95% confidence interval)	P-value
Constant	-10.625	3.839	16.527	-	<0.001
AT-III	-0.042	0.038	0.730	0.958 (0.934-0.982)	0.012
Lp-PLA2	0.063	0.024	22.725	1.077 (1.046-1.108)	<0.001
GRACE scores	0.027	0.030	6.516	1.026 (1.012-1.041)	0.028

Lp-PLA2, lipoprotein-associated phospholipase; AT-III, antithrombin III; GRACE, Global Registry of Acute Coronary Events.

increased Lp-PLA2 levels and cardiovascular events (22). The present study demonstrated results similar to those identified the literature; the results from the present study demonstrated that the Lp-PLA2 levels in the ACS group were significantly increased compared with the control group. In the ACS group, with the increase of Gensini scores, Lp-PLA2 levels exhibited an increasing trend, and there was a significant positive correlation between Gensini scores and Lp-PLA2 levels. The 3rd subgroup compared with the 4th subgroup, the Lp-PLA2 level was increased, but the difference was not statistically significant. Additional studied with larger sample sizes are required to verify these data.

Concomitantly, it has been identified that the important proinflammatory factor, thrombin, may stimulate endothelial cells to release a large number of inflammatory factors, and aggravate the progression of AS (23). The results from a previous study indicated that inhibiting the effect of ischemia on the contraction of arteries is associated with the presence of endothelial cells, nitric oxide synthesis and cyclic guanosine monophosphate activation (24). Inflammation and the formation of thrombosis mutual activation, aggravating the development of coronary heart disease and leading to the occurrence of adverse cardiovascular events (22,25,26). Long-term clinical outcomes are markedly affected by the activation of inflammation (27). Previous studies have indicated that in patients with coronary artery disease, AT-III activity is closely associated with the hypercoagulable state or thrombosis, that decreases in AT-III activity may indicate acute coronary events and that the degree of these decreases in activity levels was positively correlated with the degree of coronary stenosis (28-33). AT-III is a major inhibitor of thrombin, primarily synthesized in liver cells, vascular endothelial cells and macrophages. Generally, its anticoagulant activity is low; when the heparin or vessel walls express heparan sulfate molecules with a particular sequence of pentose and AT-III in combination, the AT-III conformation is altered, markedly increasing its anticoagulant activity (34). In cases of increased AT-III consumption or decreased synthesis, the body enters into a hypercoagulable state; this hypercoagulable state is the primary pathophysiological factor of AS and thrombosis development (35,36). In the present study, the level of AT-III activity was decreased in patients with ACS, and the decreases were most apparent in the high risk group compared with the other risk groups. Increased severity of coronary artery stenoses incurs an increase in AT-III consumption, and the body is not able to recover the deficit quickly (37). In the ACS group, with the increase of Gensini scores, AT-III activity exhibited a decreasing trend, and there was a significant negative association between AT-III and Gensini scores when comparing the 1st and 4th score quartiles.

In conclusion, Lp-PLA2 may serve as an independent risk factor for ACS, and was positively correlated with the degree of coronary artery stenosis severity. In contrast to the level of Lp-PLA2, AT-III activity was a protective factor for ACS. As the present study was a cross-sectional study, and the sample size was limited, the results require verification from additional studies using larger sample sizes.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

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

Authors' contributions

JL was responsible for study design and drafting of the manuscript. DN performed data collection. DZ and QZ performed statistical analysis. WL revised and approved the manuscript. All the authors approved the final manuscript.

Ethics approval and consent to participate

The study protocol was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University. All patients provided written informed consent.

Patient consent for publication

All patients signed an informed consent approved by the institutional Review Board.

Competing interests

The authors declare that they have no competing interests.

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