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Original Article

Lipoprotein-associated Phospholipase A2 is Associated with Angiographic Coronary Artery Disease and Coronary Artery Risk Factors in the Elderly[☆]Lini Dong¹, Xiaobing Qu¹, Zhi Gao Hu², Xiaoli Peng¹, Yanjiao Wang¹, Qin Miao¹, Xiangyu Zhang^{1*}¹ Department of Geriatrics, The Second Xiangya Hospital of Central South University, Changsha, Hunan, ² Department of Cardiology, Hainan Provincial People's Hospital, Haikou, Hainan, PR China

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SUMMARY

Background: This study investigated the correlation of lipoprotein-associated phospholipase A2 (Lp-PLA2) levels with angiographic coronary artery disease, the extent of angiographic coronary artery lesions and coronary artery disease risk factors in the elderly.**Methods:** Plasma Lp-PLA2, lipid, and high-sensitivity C-reactive protein levels were measured in 192 elderly patients who underwent coronary angiography because of suspected coronary artery disease. The extent of coronary artery lesions was recorded according to the number of vessels with lesions and the Gensini score system. The relationships of Lp-PLA2 with angiographic coronary artery disease, the extent of coronary artery lesions, and associated risk factors were assessed.**Results:** Plasma Lp-PLA2 ($359.56 \pm 133.47 \mu\text{g/L}$ vs. $215.12 \pm 58.93 \mu\text{g/L}$, $p < 0.001$), triglycerides ($1.87 \pm 1.29\text{mM}$ vs. $1.23 \pm 0.53\text{mM}$, $p < 0.001$), total cholesterol ($4.47 \pm 0.69\text{mM}$ vs. $3.59 \pm 0.75\text{mM}$, $p < 0.01$), low-density lipoprotein cholesterol ($2.52 \pm 0.91\text{mM}$ vs. $2.10 \pm 0.63\text{mM}$, $p < 0.01$), and C-reactive protein ($7.57 \pm 1.82 \text{mg/L}$ vs. $2.65 \pm 1.74 \text{mg/L}$, $p < 0.05$) were significantly higher in the angiographic coronary artery disease group compared to the controls. Lp-PLA2 increased slightly but not significantly with an increasing number of coronary artery lesions and Gensini score. Spearman correlation analysis revealed that Lp-PLA2 is positively correlated with age ($r = 0.249$, $p < 0.05$), total cholesterol ($r = 0.326$, $p < 0.01$), and low-density lipoprotein cholesterol ($r = 0.265$, $p < 0.05$). Multivariate logistic regression analysis showed that Lp-PLA2 [odds ratio, 1.03 (1.01–1.06), $p < 0.05$] and total cholesterol [odds ratio, 2.74 (1.84–7.80), $p < 0.05$] are independent predictors for angiographic coronary artery disease.**Conclusion:** Lp-PLA2 was confirmed as a risk factor for coronary artery disease and independently predicts the presence of angiographic coronary artery disease in the elderly.

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1. Introduction

Atherosclerosis is highly complex and modulated by numerous genetic and environmental risk factors. The traditional risk factors cannot explain all coronary events. Inflammation underlines

both the onset and progression of atherosclerosis. Serum markers of inflammation are involved in plaque initiation, formation and rupture^{1–3}. Recently, considerable attention has been paid to lipoprotein-associated phospholipase A2 (Lp-PLA2), which is produced by inflammatory cells and binds to low-density lipoprotein cholesterol (LDL-C) and other lipoproteins⁴. It has been considered as a new inflammatory marker and proposed to be more specific to vascular inflammation. Now, a preponderance of evidence has demonstrated a proatherogenic function for this enzyme, highlighted its importance in promoting atherosclerosis, and shown that it is an independent predictor of coronary artery disease (CAD). Elevated Lp-PLA2 is associated with an increased risk of CAD⁵ and a

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higher incidence of major adverse events at follow-up^{6–8}. However, Lp-PLA2 levels in the elderly with CAD remain poorly investigated. A few studies have demonstrated that, in the elderly, Lp-PLA2 and other inflammatory indices are potential biomarkers for vascular events, particularly CAD^{9–11}. To the best of our knowledge, there is no study on the relationship between Lp-PLA2 and angiographic CAD in elderly patients. This study aimed to evaluate the correlations between Lp-PLA2 and angiographic CAD, the extent of angiographic coronary artery lesions and CAD risk factors in the elderly.

2. Methods

2.1. Participants

The study included 192 consecutive patients older than 60 years, undergoing diagnostic coronary angiography at our hospital because of suspected CAD. All of the data regarding these patients were recorded in a structured manner that included the patients' demographic, clinical, and investigational parameters. The case notes of these patients were reviewed, and information regarding their demography, disease duration, clinical manifestations, radiological features, and treatment (medical, surgical, and interventional therapy) were retrieved. These data were systematically entered into a Microsoft Excel chart. The study was approved by the Second Xiangya Hospital of Central South University Review Board, and informed written consent was obtained from each participant. Patients were excluded if they suffered from hepatic or renal failure, rheumatic heart disease, cardiomyopathy, acute or chronic infection, malignancy, autoimmune disease, or connective tissue disease.

2.2. Blood collection and biochemical analyses

Venous blood was drawn from all patients under standardized conditions after a 12-hour fast before coronary angiography was performed. Serum samples were collected within 30 minutes and centrifuged at 3000 g for 10 minutes. Serum triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), LDL-C, high-sensitivity C-reactive protein (hs-CRP), fasting blood glucose, liver function, and renal function were measured using standard automated enzymatic methods on a Hitachi 912 automated analyzer, using reagents from Kamiya Biomedical Company (Seattle, WA, USA).

2.3. Measurement of Lp-PLA2 levels

Arterial blood was collected in EDTA-treated tubes. Plasma samples were divided into aliquots and stored at -80°C for measurement. Lp-PLA2 levels were determined using enzyme-linked immunosorbent assay (Catalogue No. E0867h; ADL, San Diego, CA, USA) according to the manufacturer's instructions. The sensitivity of the test kit was $1.0\ \mu\text{g/L}$. All samples were measured in duplicate and in a blinded fashion.

2.4. Angiographic analysis and lesion assessment

Right and left coronary angiographies were performed for each patient. Quantitative analysis of left ventricular function and coronary lesions were determined using a digital imaging system. The coronary angiograms were read by two experienced technicians blinded to patient identity, clinical diagnosis, and the study. Diagnosis of CAD was according to the following coronary angiographic analysis: no less than 50% luminal diameter stenosis either in the left main, left anterior descending, left circumflex, or right coronary

artery. Patients without CAD were defined as having $<50\%$ stenosis in all segments. Patients ($n = 192$) were divided into the CAD (124 cases) and control (68 cases) groups based on coronary angiography. The extent of CAD was quantified: (1) number of the three major coronary arteries with stenosis $>50\%$ (1-, 2-, and 3-vessel disease groups), with the left main counting as 2 vessels; and (2) Gensini score¹² [low-score (<20), intermediate-score (20–40), and high-score (≥ 40) groups]. The CAD assessment was performed blinded to the results of the blood testing.

2.5. Assessment of other parameters

Information about medical history, medication use, and cigarette smoking was obtained using standard questionnaires at the time of visit. Body mass index (BMI) was calculated by dividing the weight in kg by the square of height in m with the participants wearing light clothing and no shoes. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or antihypertensive medication use. Diabetes was defined as a fasting blood glucose >7.0 mM, clinical diagnosis of diabetes mellitus, or antidiabetic medication use.

2.6. Statistical analysis

The data were analyzed by a medical statistician using SPSS (version 16.0; SPSS Inc., Chicago, IL, USA). The descriptive data were expressed as the mean \pm standard deviation. After testing for a normal distribution of variables, Student two-tail *t* test was used for the comparisons between the paired and unpaired data, and one-way analysis of variance was used for continuous variables followed by Scheffe's test for multiple comparisons. The correlation between two variables was assessed by Spearman correlation analysis. Logistic regression models were used to evaluate the independent risk factors associated with the presence of angiographic CAD. A two-tailed $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Baseline characteristics and Lp-PLA2 levels

Baseline characteristics and Lp-PLA2 levels are shown in Table 1. There were dramatic increases in the plasma Lp-PLA2, TG,

Table 1
Baseline characteristics and lipoprotein-associated phospholipase A2 levels in the coronary artery disease (CAD) and control groups.

	CAD ($n = 124$)	Control ($n = 68$)
Age (y)	72 \pm 13	72 \pm 12
Sex (male/female) ratio	101/23	55/13
BMI (kg/m^2)	24.39 \pm 3.14	24.33 \pm 3.48
Hypertension	63 (50.80)	32 (47.05)
Diabetes	22 (17.74)	10 (14.71)
Current smoking	28 (22.58)	12 (17.64)
TC (mM)	4.47 \pm 0.69**	3.59 \pm 0.75
LDL-C (mM)	2.52 \pm 0.91**	2.10 \pm 0.63
HDL-C (mM)	1.12 \pm 0.33	1.10 \pm 0.32
TG (mM)	1.87 \pm 1.29***	1.23 \pm 0.53
hs-CRP (mg/L)	7.57 \pm 1.82*	2.65 \pm 1.74
Lp-PLA2 ($\mu\text{g}/\text{L}$)	359.56 \pm 133.47***	215.12 \pm 58.93

Data are presented as *n* (%) or mean \pm SD.

* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ compared to the control.

BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp-PLA2 = lipoprotein-associated phospholipase A2; TC = total cholesterol.

TC, LDL-C, and hs-CRP levels in the CAD group compared to the control group. No significant differences in age, sex, current smoking, history of hypertension or diabetes, or HDL-C were found between the two groups.

3.2. Relationship between Lp-PLA2 and the extent of coronary lesions

The distribution of Lp-PLA2 activity approximates a normal distribution. According to the number of the major coronary arteries with a stenosis of >50%, patients were divided into 3 groups: one-vessel ($n = 38$), two-vessel ($n = 47$), and three-vessel disease ($n = 39$). The Lp-PLA2 levels in these groups were significantly higher compared to the controls. The Lp-PLA2 levels increased slightly with the number of diseased vessels, but there was no significant difference among the three CAD groups (Table 2).

To assess the relationship between Lp-PLA2 and Gensini score, patients were divided into three classes: low score ($n = 34$), intermediate score ($n = 50$), and high score ($n = 40$). The Lp-PLA2 levels in these groups were significantly higher compared to the controls. The Lp-PLA2 levels increased slightly with the Gensini score but not significantly (Table 2).

3.3. Lp-PLA2 association with other CAD risk factors

Spearman correlation analysis revealed that the Lp-PLA2 level was positively correlated with age ($r = 0.249$, $p = 0.022$), TC ($r = 0.326$, $p = 0.002$), and LDL-C ($r = 0.265$, $p = 0.017$) but not with BMI ($r = 0.114$, $p = 0.301$), sex ($r = -0.095$, $p = 0.387$), the presence of diabetes ($r = 0.042$, $p = 0.632$) or hypertension ($r = 0.039$, $p = 0.726$), TG ($r = 0.130$, $p = 0.235$), HDL-C ($r = 0.044$, $p = 0.697$), or hs-CRP ($r = -0.066$, $p = 0.568$).

3.4. Factors that correlated with the presence of angiographic CAD

Multiple logistic regression analysis was applied to identify variables that were correlated with the presence of CAD. In univariate analysis, Lp-PLA2, TC, LDL-C, and TG had higher odds ratios in the presence of angiographic CAD, while age, sex, BMI, current smoking, diabetes, hypertension, HDL-C, and hs-CRP had lower odds ratios ($p > 0.05$). In the multivariable logistic regression model after adjusting other risk factors, Lp-PLA2 and TC were independently associated with CAD (Table 3).

4. Discussion

This study demonstrated that elevated Lp-PLA2 levels in elderly angiographic CAD patients correlates with the traditional risk factors age, TC, and LDL-C. The presence of angiographic CAD was

Table 2
Comparison of lipoprotein-associated phospholipase A2 levels in one-, two-, and three-vessel disease groups, different Gensini score groups with control group.

	Lp-PLA2 ($\mu\text{g/L}$)	ANOVA test for trend
1-vessel disease ($n = 38$)	347.42 \pm 130.37*	F = 2.669
2-vessel disease ($n = 47$)	362.69 \pm 150.73**	$p = 0.111$
3-vessel disease ($n = 39$)	365.34 \pm 124.08***	
Low-score group ($n = 34$)	340.12 \pm 139.42*	F = 2.151
Intermediate-score group ($n = 40$)	360.14 \pm 111.25*	$p = 0.148$
High-score group ($n = 50$)	370.53 \pm 135.18**	
Control ($n = 68$)	215.12 \pm 58.93	

* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ compared to the control in one-way analysis of variance followed by Scheffe's test.

Table 3
Logistic regression analysis relating variables to the presence of angiographic coronary artery disease.

	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Age (y)	1.02 (0.97–1.07)	0.494	1.08 (0.96–1.21)	0.200
Sex	1.11 (0.86–1.21)	0.513	0.16 (0.01–2.25)	0.160
BMI	1.16 (0.97–1.39)	0.100	0.81 (0.51–1.27)	0.358
Hypertension	0.71 (0.27–1.85)	0.488	0.16 (0.01–2.17)	0.169
Diabetes	0.83 (1.01–1.94)	0.491	0.21 (0.79–2.42)	0.221
Current smoking	0.93 (0.35–2.48)	0.890	0.75 (0.16–2.12)	0.452
TC	3.72 (1.74–8.00)	0.001	2.74 (1.84–7.80)	0.015
LDL-C	2.71 (1.18–6.19)	0.018	0.329 (0.05–2.17)	0.249
HDL-C	1.86 (0.28–7.18)	1.864	0.12 (0.01–7.58)	0.340
TG	2.24 (1.05–4.76)	0.037	1.41 (0.47–4.25)	0.546
hs-CRP	1.10 (0.94–1.28)	0.238	1.17 (0.96–1.44)	0.126
Lp-PLA2	1.02 (1.01–1.02)	<0.001	1.03 (1.01–1.06)	0.006

BMI = body mass index; TC = total cholesterol; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; hs-CRP = high sensitivity C reactive protein; Lp-PLA2 = lipoprotein associated phospholipase A2; CI = confidence interval; OR = odds ratio.

associated with Lp-PLA2 and TC levels, but there was no evidence that Lp-PLA2 levels increased with the burden of atherosclerosis.

The biological mechanism by which Lp-PLA2 affects the pathogenesis of atherosclerosis is not fully characterized. Recent evidence has suggested that inflammation is an important pathogenic factor in atherosclerosis and CAD, and atherosclerosis is now recognized as a manifestation of vascular inflammation^{1–3}. Lp-PLA2, formerly called platelet-activating factor acetylhydrolase, is an enzyme that is involved in lipoprotein metabolism and inflammatory pathways. It is preferentially secreted by monocytes and macrophages, which are the fundamental cells in an atherosclerotic plaque, and exists in the human circulation in combination with lipoprotein particles, in which approximately 80% combine with LDL-C⁴. The role of Lp-PLA2 is controversial. A few studies have argued that Lp-PLA2 is an antiatherosclerosis enzyme that degrades platelet activating factor and related phospholipids¹³, while others have suggested that Lp-PLA2 is proatherogenic. Its proatherogenic role is thought to be related to the hydrolysis of oxidized LDL to produce the proinflammatory mediators lysophosphatidylcholine and oxidized free fatty acid⁴, which can stimulate the secretion of cytokines from macrophages and promote plaque development.

Previous studies have revealed that serum Lp-PLA2 is significantly increased in patients with coronary endothelial dysfunction, which is recognized as an early stage of atherosclerosis¹⁴. It was remarkably expressed in human and rabbit atherosclerotic lesions, especially in the necrotic core of vulnerable plaques and surrounding macrophages¹⁵. A similar phenomenon was reported among symptomatic patients who suffered from carotid artery plaque, a marker of atherosclerotic disease^{16,17}. Most studies have examined the association between the Lp-PLA2 level and the extent of CAD assessed by coronary angiography and found that Lp-PLA2 was associated with the severity of angiographic CAD in univariable analyses^{18–21}. The association persisted after adjustment in some studies^{19–21} but was no longer significant in one study¹⁸. Lp-PLA2 levels in CAD patients were also related to the stability of atherosclerotic plaques and were independently associated with plaque rupture²². Many large population-based studies have demonstrated that high Lp-PLA2 levels are associated with a high frequency of cardiovascular events^{6–8}. These studies have provided powerful evidence to support the notion that Lp-PLA2 is crucial in plaque progression and demonstrated that increased Lp-PLA2

levels are involved in the process of atherosclerosis initiation and development and even coronary events.

Although Lp-PLA2 has been found to be a potential biomarker of CAD risk in the elderly^{9–11}, as far as we know, there is no study that has investigated the association of Lp-PLA2 with angiographic CAD and lesion severity in the elderly. Plaque morphology may change, and atherosclerotic burden may increase with age. Thus, the association of Lp-PLA2 with CAD may likewise vary with age. We therefore examined the association of Lp-PLA2 with angiographic CAD in the elderly. Our result was consistent with the above studies^{18–21}, which we found that Lp-PLA2 levels in CAD patients were also significantly higher, and Lp-PLA2 was still associated with the presence of CAD even after adjusting for traditional CAD risk factors. Our study extended the predictive value of Lp-PLA2 to the elderly and underscored the importance of Lp-PLA2 as a cardiovascular risk factor in the elderly. In contrast to the above studies, our study failed to find a correlation between Lp-PLA2 and the degree of coronary artery lesions, even though Lp-PLA2 increased slightly as the number of disease coronary artery branches and Gensini score increased. One possible reason for this difference is an important limitation in our study, which was a relatively small sample size that could prevent the result from reaching statistical significance. Another possible reason is that most of our patients received lipid-lowering therapy (data not shown) before the study. One study has demonstrated that lipid-lowering therapy had a pronounced effect on Lp-PLA2, and only when restricted to individuals not using lipid-lowering drugs was Lp-PLA2 associated with CAD severity and the number of diseased coronary vessels with significant stenosis¹⁹.

We also noted strong correlations between Lp-PLA2 and age, TC, and LDL-C, which is consistent with the published data^{10,19}. The correlations between Lp-PLA2 and TC and LDL-C were expected because approximately 80% of Lp-PLA2 is bound to LDL-C and another 7% to very low-density lipoprotein cholesterol. Because Lp-PLA2 and hs-CRP have been reported to be complementary in risk prediction, we also investigated the role of hs-CRP and failed to find a relationship with Lp-PLA2. Although hs-CRP was higher in the CAD group, multivariate models showed that Lp-PLA2 was an important predictor of the presence of CAD, while hs-CRP was not. These differences suggest that the importance of hs-CRP as a risk factor may decrease with increasing age, which is consistent with a previous study²³, or hs-CRP may affect the atherosclerotic process through pathophysiological mechanisms other than Lp-PLA2 in the elderly. Furthermore, a previous study found that hs-CRP tends to be elevated in patients with a wide range of inflammatory conditions; however, it has limitations as a specific marker for CAD²⁴. Unlike hs-CRP, the Lp-PLA2 concentration has been shown to be stable over time and not affected by systemic inflammation²⁵. Thus, Lp-PLA2 appears to be a key mediator prior to hs-CRP for predicting atherosclerosis and CAD in the elderly. This result supports further exploration of the role of Lp-PLA2 in identifying older individuals at risk for atherosclerosis and CAD.

Atherosclerosis remains the leading cause of death, myocardial infarction, and stroke, and its incidence continues to increase despite aggressive evidence-based standard treatment. This has prompted research directed at reducing the atherosclerotic burden and improving the stability of vulnerable plaques to reduce cardiovascular risk. Lp-PLA2 has a dramatic role in promoting the formation of atherosclerosis and predicting the incidence of coronary heart disease and severity of coronary artery lesions. Furthermore, animal and human studies have shown that taking oral medications that selectively inhibit Lp-PLA2 can reduce plasma Lp-PLA2 activity and stabilize the necrotic core volume^{26,27}. Thus, Lp-PLA2 may be a new target for controlling CAD and represent a

promising approach in the future, especially for the elderly who have a poor tolerance for invasive treatments.

5. Conclusion

Lipoprotein-associated phospholipase A2 was confirmed as a risk factor for CAD and independently predicts the presence of angiographic CAD in the elderly.

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