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Review Article

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# Research Progress on the Relationship between Lipoprotein Associated Phospholipase A2 and Coronary Atherosclerotic Heart Disease

**Zhang Xianmeng[1], Gao Fengmin[*1], Zhang Fuya[2], Fu Beijing[2], Wen Xin[2]**

[1]*Mudanjiang Medical University, Mudanjiang 157000, Heilongjiang*

[2]*Mudanjiang Medical University, Mudanjiang 157000, Heilongjiang*

**[*]Corresponding author**

Gao Fengmin, Department of Cardiology, Hong qi Hospital Affiliated to Mudanjiang Medical University, Heilongjiang Province, Mudanjiang 157000, Heilongjiang, China.

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## Abstract

*Coronary atherosclerotic heart disease is a common disease which seriously endangers human health. The incidence rate is increasing year by year and the age of onset is becoming younger. As a kind of Inflammatory factors of vascular, Lipoprotein associated Phospholipase A2 (Lp-PLA2) can promote the progress of inflammation and coronary atherosclerosis, and its serum level can reflect the stability of atherosclerotic plaque. Among the risk factors of coronary heart disease, Lp-PLA2, as a supplement to the traditional risk factors, has a significant reference value for the prediction of coronary heart disease. More and more studies have found that Lp-PLA2 has a significant potential value in evaluating the prognosis of coronary heart disease, especially in acute coronary syndrome patients. This review summarizes the research progress of Lp-PLA2 on the pathogenesis, detection methods, independent risk factors of predicting coronary heart disease and the treatment and prognosis evaluation of coronary heart disease.*

**Keywords:** Lipoprotein Associated Phospholipase A2, Coronary Atherosclerotic Heart Disease, Risk Factors, Acute Coronary Syndrome

## Introduction

Coronary Atherosclerotic Heart Disease (CHD) is one of the most important cardiovascular diseases threatening human health. The main pathophysiological mechanism of coronary heart disease is myocardial ischemia or necrosis caused by coronary artery stenosis or occlusion. The age of the first onset of CHD patients is generally over 40 years old. The incidence of coronary heart disease in males is earlier than that in females, and the incidence rate is higher in economically developed countries. However, compared with developing countries, the incidence rate is higher in the developed countries. Besides, nowadays we can observe that the age of coronary heart disease is younger than before. CHD is divided into chronic coronary disease and Acute Coronary Syndrome (ACS). The chronic coronary disease includes stable angina pectoris, ischemic cardiomyopathy and latent coronary heart disease, while the ACS includes unstable angina, non ST segment elevation myocardial infarction (NSTEMI), ST segment elevation myocardial infarction (STEMI) and sudden coronary death (SCD) [1]. Lp-PLA2 is also known as platelet activating factor acetyl hydrolase (PAF-AH). As a vascular specific inflammatory factor, Lp-PLA2 is mainly synthesized and secreted by inflammatory cells such as lymphocytes and macrophages, regulated by a variety of inflammatory factors throughout the body. Studies have shown that Lp-PLA2 is one of the laboratory examination index which lead to atherosclerosis and reflect the stability of atherosclerotic plaque [2]. Furthermore, Lp-PLA2 can be used as an independent risk factor for predicting coronary heart disease, meanwhile, serum level of Lp-PLA2 can also be used as an indicator for the treatment and prognosis of CHD [3]. Therefore, in this paper, the pathogenesis of Lp-PLA2 for coronary heart disease, Lp-PLA2 as an independent risk factor for predicting CHD, and the value of Lp-PLA2 in the evaluation of treatment and prognosis of CHD are summarized as follows.

## The role of Lp-PLA2 in Pathophysiology of CHD

Lp-PLA2 produces two inflammatory factors: Lysophosphatidylcholine (LPC) and free fatty acids (FFA) by hydrolyzing the acetyl group on the phospholipid glycerin scaffold of low density lipoprotein [4]. Under the action of a variety of inflammatory factors, LPC and FFA regulate the expression of CD40 ligand, adhesion factors and cytokines, and thus endothelium dependent vasodilation is impaired. Meanwhile, the two inflammatory factors men-

tioned above promote the oxidative modification process and enhance the expression of matrix metalloproteinase. Therefore, these processes not only promote inflammatory response and atherosclerosis, but ultimately lead to the formation of atherosclerotic plaque and stenosis of arterial wall. In addition, LDL was hydrolyzed by Lp-PLA2 and transformed into oxidation low density lipoprotein (OX-LDL). As a result, OX-LDL is swallowed by macrophages to form foam cells. Finally, more Lp-PLA2 was produced and released from the cells. It is worth noting that the above process is a vicious circle [5].

## Laboratory Examination Methods of Lp-PLA2

Nowadays, there are two main methods used for the detection of Lp-PLA2: one is the determination of plasma concentration, the other is the enzyme activity assay. However, the selection of detection methods for Lp-PLA2 has always been the difference between China and other countries in scientific research. On the one hand, in China, mainstream researches advocate the use of enzyme linked immunosorbent assay (ELISA) to determine the plasma concentration of Lp-PLA2. Chinese researchers believe that this method not only has excellent repeatability, but also can meet the needs of large sample detection [6]. In addition, studies recommended that Lp-PLA2<200μg/L is the normal level, 200~223μg/L is moderately elevated level, and Lp-PLA2>223μg/L is severe elevated level [7]. On the other hand, foreign studies have pointed out that this method is not as accurate as enzyme activity assay in risk stratification assessment [8]. Enzyme activity assay, also known as PLAC test, is to determine and calculate the absorbance change of the sample after a series of specific chemical reaction, which can directly reflect the activity level of Lp-PLA2, so it is favored by many foreign scholars. Besides, compared with ELISA method, PLAC test has the advantages of high accuracy and less environmental impact [9,10]. Therefore, the PLAC test, as a blood test used to measure serum activity of Lp-PLA2, was approved by the U.S. Food and Drug Administration in 2014 to predict the occurrence of cardiovascular disease [11]. In short, the two laboratory examination methods of Lp-PLA2 have their own advantages, and the selection of detection methods still needs to be comprehensively analyzed and considered according to the research needs.

Lp-PLA2 has become a Novel Independent Risk Factor for CHD

There are numerous risk factors leading to CHD, and generally accepted risk factors include dyslipidemia, hypertension, smoking, diabetes, obesity, age>40 years, gender (male) and family history of CHD [12]. In recent years, the high expression of Lp-PLA2 in atherosclerotic plaque, especially in unstable plaque, has been found by a growing number of researches [13]. A number of studies have shown that the plasma level of Lp-PLA2 is not only positively correlated with the severity of CHD, but also positively correlated with the core volume of plaque necrosis and the thickness of plaque fibrous cap [14-17]. Therefore, the enzyme activity assay was used to detect the level of Lp-PLA2, and the detection standard was established. Several studies have shown that when the serum Lp-PLA2 level is more than 225nmol/min/ml, the incidence of cardiovascular disease is significantly increased. Ultimately, 225nmol/min/ml was used as the cut-off point of Lp-PLA2, which was used to identify high risk populations of cardiovascular disease [10]. Therefore, serum level of Lp-PLA2 can be used to evaluate the stability of vulnerable atherosclerotic plaque, which is expected to become a new independent risk factor for predicting the occurrence of cardiovascular events, especially acute coronary syndrome(ACS) [18-20]. In brief, among the risk factors of CHD, Lp-PLA2 as a supplement to the original risk factors has a crucial clinical predictive value.

## Prognostic value of Lp-PLA2 in patients with CHD

Because serum level of Lp-PLA2 is significantly related to the stability of atherosclerotic plaque, Lp-PLA2 has vital potential prognostic value of CHD, especially in patients with ACS. For patients with chronic coronary disease, the level of Lp-PLA2 has a significant positive correlation with the occurrence of major adverse cardiovascular events (MACEs) in the future. In addition, serum level of Lp-PLA2 in patients with ACS was significantly higher than that in patients with chronic coronary disease [21]. What's more, serum level of Lp-PLA2 from patients with unstable angina pectoris group or non ST elevation myocardial infarction group were significantly higher than those from healthy control group, and serum level of Lp-PLA2 from patients with non ST elevation myocardial infarction group was significantly higher than that from patients with unstable angina pectoris group [22]. However, there have been numerous academic disputes about using serum Lp-PLA2 level in predicting the occurrence of MACEs in patients with ACS. One study data showed that the incidence of MACEs in higher Lp-PLA2 group was 11.8% within 6 months after PCI, while the incidence in lower Lp-PLA2 group was only 4.8%. These data highly suggest that the serum level of Lp-PLA2 in ACS patients has a certain clinical predictive value for the occurrence of MACEs within 6 months after discharge [23]. In Li et al study, Kaplan–Meier analysis showed that patients with elevated Lp-PLA2 had a lower cardiovascular event-free survival than those with lower Lp-PLA2.Meanwhile, Cox regression analysis of this study indicated that high Lp-PLA2 level, time delay from symptom onset to admission independently predicted cardiovascular event in patients with ACS after adjusting for potential confounders [24]. Maiolino et al reported that The survival without recurrent myocardial infarction rate was 81.2% in ACS patients with higher serum Lp-PLA2, which was significantly lower than that in ACS patients with lower serum Lp-PLA2. Furthermore, this study supports the use of enzyme activity assay rather than ELISA to predict the recurrence of MACEs in patients with ACS [25,26]. However, inconsistent with the above findings, one study reported that the occurrence of MACEs in postmenopausal women is related to the concentration of plasma concentration of Lp-PLA2 rather than the enzyme activity of Lp-PLA2 [27]. In O'Donoghue et al study, the researchers measured the serum levels of Lp-PLA2 in ACS patients at the beginning of onset and after 30 days of statins treatment, and the results showed that there was no significant relationship between Lp-PLA2 level and the occurrence of MACEs in ACS patients, but the high level of Lp-PLA2 measured after 30 days of statin treatment suggested a significant correlation with MACEs [28]. Similar conclusions have been drawn by Oldgren et al study, they found no association between serum level of Lp-PLA2 and cardiovascular events, and there was no significant difference between low level Lp-PLA2 group, medium level Lp-PLA2 group and high level Lp-PLA2 group [29].

Statins, as the basic drugs for patients with CHD, have the effect of regulating blood lipids of patients. Meanwhile, statins can inhibit the inflammatory reaction of vascular endothelium, and stabilize atherosclerotic plaque in order to improve the function of vascular

endothelium in ACS patients. Since the use of statins can significantly affect the serum Lp-PLA2 level, whether statins can affect the predictive value of Lp-PLA2 for CHD is also one of the focuses of current studies. In Jupiter et al study, serum level of Lp-PLA2 in ACS patients was measured at the first admission and one year after discharge, and the results showed that: the incidence of MACEs one year after discharge was significantly correlated with the level of Lp-PLA in the non-statins treatment group. However, there was no significant correlation between the incidence of MACEs and the level of Lp-PLA in the statins treatment group. Therefore, this study suggested that statins can not only significantly reduce the level of Lp-PLA2, but also interfere with the predictive value of Lp-PLA2 [30]. However, in other study, after 6 months of conventional dose of statins, the level of Lp-PLA2 was decreased in patients with CHD. At the same time, the study indicated that the incidence of MACEs was significantly correlated with the level of Lp-PLA in these patients treated with statins [31].

By further analyzing and comparing the similarities and differences of the research process and methods of the above studies, the main reasons for the differences and controversies are as follows: Firstly, there are differences in the selection of detection methods for Lp-PLA2 level among these studies. In some studies, the serum level of Lp-PLA2 was determined by ELISA, while in others, the Lp-PLA2 was measured by enzyme activity assay. Secondly, the time window of detecting serum level of Lp-PLA2 was different among these studies. Thirdly, the inclusion criteria of patients were different among the studies, mainly reflected in the selection of patients with ACS. Some studies only included patients with unstable angina, non ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction. Fourthly, there are individual differences between studies groups, including race, other clinical complications and so on. Last but not least, the treatment measures of different study groups were different during the study period.

## Discussion

CHD is the leading cause of death and disability in human. Lp-PLA2, as a vasoinflammatory factor, is found as a laboratory examination index. Nowadays, the relationship between Lp-PLA2 and CHD has attracted the attention of numerous medical experts. The mechanism of Lp-PLA2 in the formation of atherosclerotic plaque has been explained clearly. Meanwhile, the detection technology of Lp-PLA2 is gradually becoming mature including the ELISA to determine the plasma concentration of Lp-PLA2 and the PLAC to measure the enzyme activity assay. Numerous studies have indicated that Lp-PLA2 level is expected to become a new independent risk factor for cardiovascular events, especially ACS. Since serum level of Lp-PLA2 is significantly related to the stability of atherosclerotic plaque, the evaluation of the prognosis of CHD by Lp-PLA2 has become the focus of the studies. Due to the influence of different Lp-PLA2 detection methods, inclusion criteria and treatment measures of patients, the experimental results are controversial among these studies. Therefore, whether the level of Lp-PLA2 can be an independent predictor of recurrence of MACEs in patients with ACS still needs more studies to solve and confirm.

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