Lipoprotein-associated phospholipase A$_2$, vascular inflammation and cardiovascular risk prediction

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Abstract: Circulating lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) is a marker of inflammation that plays a critical role in atherogenesis; its inhibition may have antiatherogenic effects. Studies from the West of Scotland Coronary Prevention Study (WOSCOPS), Monitoring Trends and Determinants in Cardiovascular Diseases (MONICA) and Rotterdam cohorts have shown that Lp-PLA$_2$ is an independent predictor of coronary heart disease (CHD), and the association is not attenuated upon multivariate analysis with traditional risk factors and other inflammatory markers. Studies in subjects with coronary artery disease (CAD) have also shown associations between Lp-PLA$_2$ and cardiovascular risk. At least two recent studies have shown that Lp-PLA$_2$ is a risk predictor for stroke. Overall, epidemiological studies suggest that measurement of Lp-PLA$_2$ in plasma may be a useful in identifying individuals at high risk for cardiovascular events.

Keywords: Inflammation, vascular, cardiovascular risk, coronary, stroke

Introduction

Circulating markers of inflammation may predict cardiovascular risk. Lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) is a macrophage-derived enzyme from the phospholipase A$_2$ superfamily that has been shown to be an independent predictor of cardiovascular disease (CVD) and future events. Several epidemiological and clinical studies have examined the role of Lp-PLA$_2$ in CVD, and in the aggregate, the evidence suggests a role for the use of this biomarker in risk prediction.

The role of Lp-PLA$_2$ in atherosclerosis

Lipoprotein-associated phospholipase A$_2$, also known as platelet activating factor acetylhydrolase (PAF-AH), is a 50 kD Ca^{2+}-independent phospholipase, distinct from another macrophage product, secretory PLA2, a 14kD Ca^{2+}-dependent enzyme (Dada et al 2002). Lp-PLA$_2$ is expressed in atherosclerotic plaques (Hakkinen et al 1999), and in macrophages within the fibrous cap of human rupture prone lesions (Kolodgie et al 2004). Lp-PLA$_2$ is transported in plasma predominantly associated with low density lipoprotein (LDL) (Caslake et al 2000). Lp-PLA$_2$ causes hydrolysis of modified phospholipids within oxidized LDL (OxLDL), generated by LDL oxidation in the milieu of the artery wall (MacPhee et al 1999; Ross 1999; MacPhee 2001), resulting in the production of lysophosphatidylcholine (LysoPC) and oxidized fatty acids (OxFA) (MacPhee et al 1999). The proinflammatory and atherogenic properties of LysoPC are well known (Quinn et al 1988; MacPhee et al 1999).

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Lp-PLA$_2$ modulation by pharmacological interventions

Preclinical studies have shown that inhibition of Lp-PLA$_2$ significantly reduces atherogenesis (MacPhee 2001). Initial clinical studies suggest that the inhibitors of Lp-PLA$_2$ can block enzyme activity in plasma and within atherosclerotic plaques (MacPhee et al 2005). Statins and fibrates are known to decrease cardiovascular events and reduce plasma Lp-PLA$_2$ levels (Tsimihodimos et al 2003; Schaefer et al 2005). There appears to be differences among the statins, with atorvastatin being more effective than fluvastatin, lovastatin, pravastatin, or simvastatin for decreasing not just LDL-cholesterol, but also high sensitive C-reactive protein (hs-CRP) (32% reduction with atorvastatin) and Lp-PLA$_2$ (26% reduction with atorvastatin) (Schaefer et al 2005).

Assessment of Lp-PLA$_2$ Levels

Lp-PLA$_2$ mass is measured by an enzyme immunoassay in human plasma (the PLAC™ test) (Dada et al 2002). In addition, Lp-PLA$_2$ activity can also be measured in human plasma (Tselepis et al 2002).

Cardiovascular risk prediction in clinical studies

WOSCOPS (The West of Scotland Coronary Prevention Study) was a primary prevention trial designed to evaluate the use of pravastatin in hypercholesterolemic men (Packard et al 2000) (Table 1). A 2-fold greater risk of coronary heart disease (CHD) was observed for patients in the highest quintile of Lp-PLA$_2$ levels compared with those in the lowest quintile. Similar to Lp-PLA$_2$, the risk of CHD was 2-fold greater in the highest quintile of CRP levels and white-cell count compared with the lowest quintile. However, on multivariate analysis, risk associated with CRP levels and white-cell counts was attenuated, but the association of Lp-PLA$_2$ with risk of CHD remained significant for all quintiles (p=0.005), demonstrating the strength of Lp-PLA$_2$ as an independent marker of CHD. Of note, Lp-PLA$_2$ was the only marker of inflammation whose levels were not affected by smoking.

The ARIC study (Atherosclerosis Risk in Communities) (Ballantyne et al 2004) was a prospective study designed to evaluate atherosclerosis over a period of 6 years in over 12 000 apparently healthy middle-aged men and women. In a case-cohort analysis, a hazard ratio (HR) of 1.78 (95% confidence index [CI], 1.33–2.38) for the highest tertile of Lp-PLA$_2$ ($\geq$422 µg/L) and HR 2.53 (1.88 to 3.40) for the highest tertile of CRP (>3.0 mg/L) was reported. In patients with LDL levels below the median (<130mg/dL), both Lp-PLA$_2$ and CRP levels were significantly and independently associated with CHD, even in fully adjusted models. Those individuals with increased levels of both Lp-PLA$_2$ and CRP were found to have the greatest risk for a CHD event (HR 2.95 CI, 1.47–5.94]).

In a Southern German study examining subjects from the MONICA (Monitoring Trends and Determinants in Cardiovascular Diseases) population, the relationship between Lp-PLA$_2$ levels and risk of coronary events was evaluated in 934 healthy men aged 45 to 64 years who were followed for 14 years (Koenig et al 2004). In the 97 men who suffered a coronary event, mean baseline levels of Lp-PLA$_2$ were significantly higher in men who had suffered an event. A 1 standard deviation (SD) increase in Lp-PLA$_2$ mass

Table 1 Studies and trials demonstrating significant independent association between Lp-PLA$_2$ levels and cardiovascular endpoints, expressed either as HR (highest compared with lowest tertile, quartile, or quintile) or RR per 1 SD

Author	Population	Endpoints	Risk
			HR
Ballantyne	ARIC: Healthy subjects	Coronary events	2.08 (LDL<130)
Ballantyne	ARIC: Healthy subjects	Stroke	1.97
Khusiyenova	Southern Germans: CAD	Presence of CAD	1.84
Oei	Rotterdam: Elderly	Coronary events/stroke	1.96/1.95
			RR per 1 SD
Packard	WOSCOPS: Hypercholesterolemia	Cardiac events	1.18
Brilakis	Mayo Clinic study: CAD	Cardiac events	1.27
Iribarren	CARDIA: Young adults	Coronary calcification	1.25
Koenig	MONICA: Healthy men	Coronary events	1.21

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CAD, coronary artery disease; CARDIA, Coronary Artery Risk Development in Young Adults; HR, hazard ratio; LDL, low-density lipoprotein; MONICA, Monitoring Trends and Determinants in Cardiovascular Diseases; RR, risk ratio; SD, standard deviation; WOSCOPS, West of Scotland Coronary Prevention Study.

was associated with a 37% increase in risk of future coronary events, even after controlling for potentially confounding factors and CRP. The combination of a high Lp-PLA$_2$ (>290.8 µg/L) and a high CRP (>3 mg/L) was consistently associated with a statistically significantly increased risk for future coronary events, suggesting that these biomarkers may be complementary in identifying high-risk subjects.

The Rotterdam Study was a population-based follow-up study in 7983 subjects aged 55 years and over. Oei et al (2005) performed a case-cohort study, including 308 CHD cases, and a random sample of 1820 subjects. Compared with the first quartile of Lp-PLA$_2$ activity, multivariate-adjusted HRs for CHD for the second, third, and fourth quartiles were 1.39 (95% CI, 0.92 to 2.10), 1.99 (95% CI, 1.32 to 3.00), and 1.97 (95% CI, 1.28 to 3.02), respectively (p for trend=0.01). The Rotterdam study thus provides additional evidence for an association between Lp-PLA$_2$ and CHD, independent of other risk factors.

One small study (Blake et al 2001) failed to show an independent association between Lp-PLA$_2$ levels and risk of CHD. In univariate analysis, mean levels of Lp-PLA$_2$ were significantly higher at baseline among cases than controls, but the predictive value of Lp-PLA$_2$ was attenuated after adjustment for other cardiovascular risk factors. This study examined a small number of women, many of whom were on hormonal therapy, which may explain the disparate observations in this study compared with others showing a relationship between Lp-PLA$_2$ levels and risk of CHD.

Studies of Lp-PLA$_2$ in patients with angiographic evidence of coronary artery disease

In a study of 148 men, 48 with angiographically proven coronary artery disease (CAD), 46 who had suffered myocardial infarction at least 1 year prior to the study, and 54 normal aged-matched controls (Caslake et al 2000), elevated levels of Lp-PLA$_2$ were found in patients with angiographic CAD compared with the normal patients, independent of LDL and other risk factors including smoking and systolic blood pressure. Another study (Khyseyinova et al 2005) in German patients with angiographic evidence of CAD and in age- and gender-matched blood donors confirmed that Lp-PLA$_2$ concentrations were significantly higher in cases than in controls; further age and gender adjusted odds ratio (OR) for the presence of CAD was 1.61 (95% CI, 1.07–2.44) when the top quartile of the Lp-PLA$_2$ distribution was compared

with the bottom quartile. Adjustment for traditional cardiovascular risk factors and statin intake resulted in an OR of 2.04 (1.19–3.48). An additional study (Brilakis et al 2005) in 504 patients at the Mayo Clinic undergoing clinically indicated coronary angiography, demonstrated higher Lp- PLA$_2$ levels were associated with a greater risk of events: the HR per SD was 1.28 (95% CI, 1.06–1.54, p=0.009), and remained significant after adjusting for clinical and lipid variables and CRP.

Lp-PLA$_2$ in young adults with coronary artery calcification

The association between Lp-PLA$_2$ (mass and activity), and coronary artery calcification (CAC) in young adults was examined in a nested case-control study using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study (Iribarren et al 2005). Lp-PLA$_2$ mass and activity were significantly higher in cases than in controls. The OR of calcified coronary plaque per 1 SD increment was 1.40 (1.17 to 1.67) and 1.39 (1.14 to 1.70) for Lp-PLA$_2$ mass and activity, respectively; the relationship was independent of LDL-cholesterol. After adjusting for multiple covariates, a statistically significant association remained for Lp-PLA$_2$ mass (1.28; 95% CI, 1.03–1.60) but not for activity. Thus, Lp-PLA$_2$ (measured as mass) appears to be involved in early CAC.

Lp-PLA$_2$ as a risk predictor for stroke

Recently, Oei et al (2005) compared 110 ischemic stroke cases with a random sample of 1820 subjects in a case-cohort analysis in the Rotterdam study, and also reported a significant association between Lp-PLA$_2$ activity and ischemic stroke. Compared with the first quartile of Lp-PLA$_2$ activity, multivariate-adjusted HRs for ischemic stroke were 1.08 (95% CI, 0.55 to 2.11), 1.58 (95% CI, 0.82 to 3.04), and 1.97 (95% CI, 1.03 to 3.79) (p for trend=0.03). In a further analysis from the ARIC study, the relation between Lp-PLA$_2$, CRP, traditional risk factor (RFs), and stroke over 6 years was examined (Ballantyne et al 2005). Both Lp-PLA$_2$ and CRP were associated with stroke after adjustment for age, sex, and race with a HR of 2.16 for the highest versus the lowest tertile of Lp-PLA$_2$ and 2.64 for CRP. In a model including CRP and Lp-PLA$_2$ with traditional RFs plus body mass index (BMI), triglycerides, and antihypertensive medication, the highest tertile of Lp-PLA$_2$ had an HR of 2.04 (1.23–3.38, p<0.01). Individuals

with high levels of both CRP and Lp-PLA$_2$ were at the highest risk after adjusting for traditional risk factors.

Thus, both Lp-PLA$_2$ and CRP may be complementary beyond traditional risk factors in identifying individuals at increased risk for stroke. Inflammation may play a role in the etiology of stroke, reflected at least in some patients by elevated levels of inflammatory biomarkers, and antiinflammatory properties of statins may be crucial to their beneficial effects on stroke reduction.

Conclusions

Lp-PLA$_2$ plays a critical role in atherogenesis, and may indeed be a marker of inflammation (Sudhir 2005). Inhibition of Lp-PLA$_2$ may have antiatherogenic effects. Studies from the WOSCOPS and MONICA cohorts have shown that the association of Lp-PLA$_2$ with CHD is not attenuated upon multivariate analysis with other inflammatory markers and traditional risk factors. Two recent studies have shown that Lp-PLA$_2$ is a predictor of stroke risk. Measurement of Lp-PLA$_2$ in plasma may be useful in identifying subjects at high risk for future cardiovascular events.

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