Lipoprotein-Associated Phospholipase A2 and Cardiovascular Risk
State of the Evidence and Future Directions
Carlos Iribarren

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Yang and colleagues provide new evidence that Lp-PLA2 is an independent correlate of coronary endothelial-dependent dysfunction in a sample of 172 patients with no significant coronary artery disease (<30% stenosis) undergoing diagnostic coronary angiography. Microvascular and epicardial endothelial-dependent dysfunction were assessed as change in coronary blood flow and change in coronary artery diameter in response to intracoronary acetylcholine, respectively. After adjustment for relevant covariables, the odds ratio for either type of endothelial-dependent dysfunction in the highest tertile of Lp-PLA2, compared with the lowest tertile, was 3.3 (95% CI, 1.6 to 6.6), making the association unlikely to be attributable to confounding factors. Moreover, the association remained strong in subgroup analysis among patients not taking lipid lowering medication. This additional analytical step is important because statin therapy has been shown to reduce Lp-PLA2 levels. On the other hand, no relation was found between Lp-PLA2 levels and endothelial-independent dysfunction measured as change in coronary artery diameter in response to intracoronary nitroglycerin.

Why is this study significant? First, this report demonstrates for the first time a possible involvement of Lp-PLA2 in endothelial-dependent dysfunction and begins to unravel likely pathways driving the associations observed in many epidemiological studies focusing on Lp-PLA2 and cardiovascular events. Lp-PLA2 is believed to be a promoter of inflammation through generation of lysophosphatidyl choline and oxidized free fatty acids (see schematic Figure). Lysophosphatidyl choline in turn suppresses release of nitric oxide (which may explain its potential effect on endothelial function) and upregulates CD40 ligand expression in T lymphocytes. Second, these findings are in agreement with recent data from the CARDIA study showing an independent association between Lp-PLA2 and coronary artery calcification, another marker of subclinical coronary artery disease. Increased coronary artery calcium scores have been shown to be associated with coronary endothelial dysfunction. These studies taken together support the notion that Lp-PLA2 may be implicated in the initiation and progression of atherosclerosis. Third, the link between Lp-PLA2 and endothelial dysfunction may help explain the recently observed association between Lp-PLA2 and ischemic stroke, because endothelial function is a proven risk factor for ischemic stroke. Finally, in vitro studies indicate that Lp-PLA2 activity is preferentially associated with the atherogenic small dense (sdLDL) particles, which have been shown to be independently predictive of endothelial function.

Consistent with prior reports, no correlation existed between Lp-PLA2 and C-reactive protein (CRP) in the study by Yang et al. This means that these two biomarkers may be capturing nonoverlapping aspects of the inflammatory response: whereas CRP is a systemic acute phase reactant, Lp-PLA2 may be more specific for vascular inflammation. Despite mounting evidence that Lp-PLA2 may be etiologically involved in atherosclerosis development, there are many questions that remain unanswered. For example, what is more informative, measuring enzymatic mass, enzymatic activity, or a combination of both? What is the value of Lp-PLA2 as a cardiovascular risk marker in understudied minority populations such as Hispanics, East Asians, and South Asians? Is Lp-PLA2 associated with cardiovascular risk independently of small-dense LDL? Is Lp-PLA2 related to noninvasive flow-mediated vasodilation? Can Lp-PLA2 levels be modified by diet or exercise? What is the threshold of Lp-PLA2 elevation at which risk becomes clinically relevant? To what extent is the effect of Lp-PLA2 on atherosclerotic disease risk mediated through downstream elevation of lysophosphatidyl choline? What is the role of Lp-PLA2 in plaque stability and in how coronary artery disease is first manifested (as either stable exertional angina or as acute myocardial infarction)? Is Lp-PLA2 an independent risk factor for heart failure? What is the prognostic value of genetic variation in the Lp-PLA2 gene? Do polymorphisms in
the Lp-PLA2 gene interact with other atherogenic genetic polymorphisms or with environmental factors? These are questions that cardiovascular epidemiologists and clinicians will have to contend with over the next few years.

Another intriguing area of Lp-PLA2 is that it may be a viable therapeutic target. A small molecule inhibitor is being developed, with encouraging properties. Ultimately, although Lp-PLA2 seems to be coming of age as a marker of cardiovascular risk, its ultimate value as a cost effective risk marker (above and beyond traditional cardiac risk factors) and as a potential therapeutic target await evidence from randomized clinical trials.

References
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