Lipoprotein-associated phospholipase A2, a marker of vascular inflammation and systemic vulnerability

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This editorial refers to `Expression of lipoprotein-associated phospholipase A2 in carotid artery plaques predicts long-term cardiac outcome', by J. Herrmann et al. on page 2930

As interventional cardiologists, we are sometimes prone to believe that plaque quantity, more than plaque biology, is a determinant of patients’ prognosis. This concept is unfortunately challenged in daily practice, as accelerated progression of atherosclerosis, rupture of a plaque that was not critical at angiography, and/or dynamic phenomena such as spasm contribute to determine the patient’s prognosis. That the extent and severity of coronary artery disease at angiography is a strong prognostic index for the risk of subsequent (cardio)vascular events is not under discussion. However, our understanding of plaque progression and instability remains far from complete. In line with this concept, Lavi et al. recently reported that the presence of an abnormal coronary reactivity to an endothelium-dependent stimulus identifies areas occupied by plaques with a larger necrotic core, i.e. at higher risk for rupture. In addition, a number of studies and anecdotal evidence have shown that endothelial dysfunction and/or oxidative stress, systemic or local, may predict disease progression/instability and overall patient prognosis. Although it needs to be acknowledged that the best therapeutic strategy for plaques that are histologically vulnerable but cause no severe stenosis at angiography remains unexplored, the search for new markers and techniques that help in detecting vulnerable plaques and vulnerable patients should be considered a priority of modern cardiology.

An effort in this direction is presented by Herrmann et al. who describe the important role of lipoprotein-associated phospholipase A2 (Lp-PLA2) levels and activity, as measured at the level of carotid plaques, in predicting future cardiovascular events. This concept provides further support for the idea that atherosclerosis is a systemic disease, and that plaque activation in a given vascular district is associated with a global increased cardio- or cerebrovascular risk. PLAs belong to a superfamily that contains 15 separate groups and a number of subgroups characterized on the basis of sequence, molecular weight, disulfide bonds, requirement for Ca²⁺, and other molecular and functional features. Five major categories of PLAs are usually described: these include the secreted small molecular weight sPLA₂, the larger cytosolic Ca²⁺-dependent cPLA₂, the Ca²⁺-independent iPLA₂, the platelet-activating factor acetylhydrolases, and the lysosomal PL A₂. In general, PLA₂ hydrolyse the fatty acid from the sn-2 position of membrane phospholipids. The two compounds that result from this reaction are a polyunsaturated fatty acid that functions as substrate for a number of enzymes to form various eicosanoids and eicosanoid-related mediators and a lysophospholipid which can also have important roles in biological processes. Lysophospholipids such as lysophosphatidylcholine may also serve as markers of local PLA₂ activity, although, as Herrmann et al. acknowledge, one needs to keep in mind that the production of these mediators is not exclusive to these enzymes. Thus, products of PLA₂ activity may mediate a variety of biological events, and crucial roles during signalling and metabolic processes such as host defence, inflammation, and innate immunity have been described for most of the members of this superfamily.

Platelet-activating factor acetylhydrolases are composed of two PLA₂ groups, and are mostly produced by macrophages and activated inflammatory cells. One member of this group is the Lp-PLA₂, a 45 kDa, Ca²⁺-independent secreted enzyme that catalyses a number of reactions of biological importance and that, notably, is able to bind to both HDL and LDL cholesterol molecules through as yet incompletely understood mechanisms. The physiological role of Lp-PLA₂ and its potential role in determining cardiovascular pathology is also far from being completely understood (Figure 1), and there are lines of evidence suggesting both an anti-inflammatory and a proinflammatory function of this enzyme. In human plasma, the majority of the Lp-PLA₂ activity is present as a complex with LDL and lipoprotein(a). In particular,
Lp-PLA2 appears to be particularly represented in small dense LDL particles, which are believed to be more proatherogenic and to promote Lp-PLA2 activity. Bound to these lipoproteins, according to the hypothesis recently proposed by Stafforini et al., Lp-PLA2 hydrolyses potentially dangerous oxidized phospholipids, reducing their ability to promote monocyte chemotaxis and adhesion, and it decreases the bioavailability of the prothrombotic platelet-activating factor. Thus, in a physiological state, Lp-PLA2 might actually have a protective, anti-inflammatory and antiplatelet function, as demonstrated by evidence in animal in vivo studies in which overexpression of human plasma PLA2 retarded the progression of conditions associated with cardiovascular disease, including atherosclerosis and post-ischaemic injury. Similarly, genetic deficiency of PLA2 has been associated with increased incidence and severity of cardiovascular conditions in certain (prevalently Asian) populations. Interestingly, other lines of evidence suggest that Lp-PLA2 might also have a proatherogenic role, as the bioproducts of the Lp-PLA2-mediated hydrolysis of oxidized phospholipids are also proinflammatory moieties, such as lysophosphatidylcholine and oxidized fatty acids, which might have an important role in inflammation. In particular, lysophosphatidylcholine has been shown to be involved in inflammatory cytokine production, in the induction of the expression of adhesion molecules and cytokines, it has a chemoattractant property for macrophages, and it induces vascular smooth muscle migration. Interestingly, the PLA2-mediated release of these compounds might be involved in a deleterious feed-forward mechanism whereby recruitment of macrophages, T-cell lymphocytes, and mastocytes in activated plaques may lead to further Lp-PLA2 production and activity. This hypothesis of a proatherogenic role for Lp-PLA2 appears to be supported by evidence from immunohistochemical studies suggesting preferential upregulation of Lp-PLA2 within the necrotic core and in macrophages surrounding vulnerable and ruptured plaques as compared with stable ones. Finally, another possibility has been proposed for the role of PLA2 in atherogenesis: in the presence of excessive levels of superoxide anion and nitric oxide, the formation of peroxynitrite, a potent mediator involved in endothelial dysfunction and atherogenesis, might lead to oxidative inhibition of the Lp-PLA2. This peroxynitrite-induced inhibition, concomitant with lipid oxidation, would cause the accumulation of oxidized phospholipid species that can form phospholipid–protein adducts whose high immunogenic and proinflammatory potential further contributes to determine atherogenesis. Substantiating the involvement of PLA2 in atherogenesis, increased mass and/or activity of Lp-PLA2 have been associated (with some negative findings) with various cardiovascular endpoints in healthy subjects and patients with acute coronary syndromes, and a consistently positive association between Lp-PLA2 and cardiovascular
risk has been reported in patients with stable coronary artery diseases.\textsuperscript{5,12,13} Collectively, these data suggest that Lp-PLA\textsubscript{2} might be a reliable biomarker of cardiovascular risk in various populations and that it might help in guiding the intensity of preventive therapy. Since Lp-PLA\textsubscript{2} may be both a specific marker and a causal mediator of plaque progression and instability, a more exciting perspective is to test the possibility of using it as a therapeutic target. The development of the specific oral Lp-PLA\textsubscript{2} inhibitors, the azetidinones, has opened up this possibility: therapy with the Lp-PLA\textsubscript{2} inhibitor darapladib has been associated, in animal models and patients with cardiovascular disease, with a reduction (or reduced progression) of atherosclerosis and of some morphological markers of plaque instability.\textsuperscript{14,15} although no effect was shown on plaque deformability and other parameters of plaque instability. Thus, until further studies are performed, it needs to be acknowledged that our understanding of the role of Lp-PLA\textsubscript{2} in atherogenesis, inflammation, and oxidative stress remains incomplete, and that most of the knowledge to date is founded on evidence of association more than causation. The study by Herrmann et al.\textsuperscript{5} adds further important information, and it emphasizes the fact that most of the knowledge to date is founded on evidence of association more than causation. In this perspective, invasive or minimally invasive techniques would definitely benefit from a molecular imaging biomarker that allows the study of plaque composition and characteristics in a safe and reliable way. In this perspective, invasive or non-invasive technologies that allow identification of biological markers of instability in single plaques are eagerly awaited.

**Conflict of interest:** none declared.

**References**


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