LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A2: EFFECTS OF LOW DENSITY LIPOPROTEIN APHERESIS

Patrick M. Moriarty, M.D., FACP, Director, Atherosclerosis and LDL-Apheresis Center, University of Kansas Medical Center, 1336 KU Hospital, 3901 Rainbow Blvd., Kansas City, KS 66160-7374, E-mail: pmoriart@kumc.edu, Tel: (913) 588-6057, Fax: (913) 588-4074, www.ldlapheresis.org

Introduction

In addition to hypercholesterolemia, chronic arterial inflammation has been shown to be strongly associated with atherosclerosis and cardiovascular disease (CVD) [1]. The accumulation and oxidation of LDL within the intima trigger inflammatory processes within the vessel wall. Certain markers of inflammation, such as C-reactive protein (CRP), soluble CD40 ligand (sCD40L), oxidized LDL, and lipoprotein-associated phospholipase A2 (Lp-PLA2) have emerged as novel and potentially useful markers in identifying patients with an increased risk of CVD. These inflammatory markers not only predict the long-term risk of CVD but recently have been added to the Thrombolysis in Myocardial Infarction (TIMI) risk score for enhanced risk stratification in the setting of acute coronary syndrome. Therapies that specifically target such inflammatory markers may help to reduce the inflammatory response, stabilize atherosclerotic plaques, and optimize the treatment options for patients at high risk of CVD.

Lp-PLA2

Lp-PLA2 is an enzyme mainly produced by monocytes, macrophages, T-lymphocytes, and the liver. In the vasculature, about 70% of Lp-PLA2 is bound to LDL-C and is found within atherosclerotic plaques. Lp-PLA2 is involved in the oxidative modification of LDL by hydrolyzing oxidized phosphatidylcholines, producing lysophosphatidylcholine and oxidized free fatty acids, both of which are proinflammatory and assist in the formation of atherosclerotic plaques. Recent studies have shown Lp-PLA2 to be an independent marker for coronary endothelial dysfunction [2] and coronary artery disease [3]. Lp-PLA2 activity is also a marker for the atherogenic small, dense LDL particles in human plasma [4].

Potential pharmacological therapies may reduce the pro-atherogenic effects of Lp-PLA2 by blocking enzyme activity in plasma and within the atherosclerotic plaques themselves. However, in some high-risk patients, dangerously high cholesterol levels may persist, or the patient may not tolerate the pharmacological treatments. For such patients, there is an unmet
need for alternative means of lowering cholesterol and levels of pro-inflammatory markers such as Lp-PLA₂.

**LDL apheresis**

LDL apheresis is a medically approved device for the lowering of plasma cholesterol in patients with hypercholesterolemia and who are unsuitable for pharmacological treatment (see Figures 1a, 1b). The technique is approved for use in patients with uncontrolled hypercholesterolemia (LDL > 200 mg/dl) and CVD, or hypercholesterolemia (> 300 mg/dl) without CVD. Treatments occur weekly or biweekly depending on level of plasma cholesterol and severity of CVD. The most common LDL apheresis methods include LDL immunoabsorption, dextran sulfate cellulose (DSA), heparin extracorporeal LDL precipitation (HELP), and direct adsorption of lipoprotein (DALI). Only the DSA and HELP are approved in the United States and their ability to lower plasma cholesterol is related to the binding of ApoB-lipoproteins to the dextran sulfate filter (DSA) or precipitation of positively charged ApoB-lipoproteins when heparin is added at a low pH (HELP). The DALI system, which treats whole blood, removes LDL-C by adsorption onto polycrylate-coated beads. Immunoadsorption removes plasma cholesterol by columns of polyclonal sheep antibodies to human apoB₁₀₀.

LDL apheresis can lower LDL-C by 60%-80% [5] and can significantly modify a host of other vascular markers and pathologic processes associated with systemic inflammation (see Table 1) and CVD. Such markers include C-reactive protein, tissue factor, fibrinogen, soluble CD40 ligand, and Lp-PLA₂ [6]. The mechanism for the reductions of these markers is not fully understood but is believed to be similar to the removal of lipoproteins.

**Effects of LDL Apheresis on Lp-PLA₂**

Moriarty and Gibson have recently examined the reduction of Lp-PLA₂ acutely and chronically in patients with familial hypercholesterolemia and CVD [7]. After treatment with LDL apheresis every two weeks for ≥ three months, levels of Lp-PLA₂ were acutely reduced by 32% and chronically decreased pre-treatment levels by 22% (p < 0.003). In addition, there was no significant correlation between LDL cholesterol and Lp-PLA₂ (rₛ = 0.32, p = 0.06), indicating that chronic LDL apheresis reduces Lp-PLA₂ independent of LDL cholesterol and may represent another means of reducing the risk of cardiovascular events.

CRP has also been revealed to lower both acutely (65%) and chronically (12%-48%) [8,9] by LDL apheresis. Like Lp-PLA₂, the reduction of CRP is not correlated to the lowering of LDL-C. Interestingly, fibrinogen, another marker of inflammation, is acutely reduced by 65% following apheresis (HELP) but has not demonstrated significant chronic reduction as seen by CRP and Lp-PLA₂. The lack of chronic reduction for fibrinogen occurs despite the plasma protein having a longer ½-life (>100 hours) [10] than CRP (< 20 hours [11]. To explain the difference in chronic reduction of these inflammatory markers, Otto suggested the discrepancy between CRP and fibrinogen may be a reflection of the stronger association of CRP concentration with the inflammatory activity of atherosclerotic lesions compared to fibrinogen.

**Conclusions**
The identification of novel inflammatory markers involved in the etiology of atherosclerosis may help in determining levels of CVD risk and potential therapeutic approaches to treat the condition. Lp-PLA2 is a novel inflammatory marker of cardiovascular risk and its inhibition or reduction is a potential therapeutic target in the treatment of atherosclerosis. LDL apheresis is an additional, non-pharmacological, treatment option in patients with familial hypercholesterolemia and who have a very high risk of developing CVD and there is evidence that LDL apheresis can acutely and chronically reduce Lp-PLA2 levels independently of LDL cholesterol reduction. These findings may represent a potential mechanism by which LDL apheresis can reduce the risk of CVD in selected populations such as the acute coronary patient.

References

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<th>Marker</th>
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<td></td>
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<tr>
<td>CRP</td>
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MCP-1 = monocyte chemoattractant protein-1  
MMP-9 = matrix metalloproteinase-9  
TIMP-1 = tissue inhibitor of metalloproteinase-1  
ET-1 = endothelin-1  
LBP = lipopolysaccharide binding protein  
sCD40L = soluble CD40 ligand  
Lp-PLA₂ = Lipoprotein-Associated Phospholipase A₂  
sCD430L = soluble CD40 ligand  
VCAM-1 = Vascular Cellular Adhesion Molecule-1  
CRP = C Reactive Protein  
--- = no data available
Figure 1a: Schematic Illustrating the Apheresis Process (Liposorber)

Figure 1b: Flow diagram of the Heparin-induced Extracorporeal Low-density Lipoprotein Precipitation (HELP) system