Percutaneous Coronary Intervention Results in Acute Increases in Oxidized Phospholipids and Lipoprotein(a) Short-Term and Long-Term Immunologic Responses to Oxidized Low-Density Lipoprotein

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Background—This study was performed to assess whether oxidized low-density lipoprotein (OxLDL) levels are elevated after percutaneous coronary intervention (PCI).

Methods and Results—Patients (n=141) with stable angina pectoris undergoing PCI had serial venous blood samples drawn before PCI, after PCI, and at 6 and 24 hours, 3 days, 1 week, and 1, 3, and 6 months. Plasma levels of OxLDL-E06, a measure of oxidized phospholipid (OxPL) content on apolipoprotein B-100 detected by antibody E06, lipoprotein(a) [Lp(a)], autoantibodies to malondialdehyde (MDA)-LDL and copper-oxidized LDL (Cu-OxLDL), and apolipoprotein B-100–immune complexes (apoB-IC) were measured. OxLDL-E06 and Lp(a) levels significantly increased immediately after PCI by 36% (P<0.0001) and 64% (P<0.0001), respectively, and returned to baseline by 6 hours. In vitro immunoprecipitation of Lp(a) from selected plasma samples showed that almost all of the OxPL detected by E06 was bound to Lp(a) at all time points, except in the post-PCI sample, suggesting independent release and subsequent reassociation of OxPL with Lp(a) by 6 hours. Strong correlations were noted between OxLDL-E06 and Lp(a) (r=0.68, P<0.0001). MDA-LDL and Cu-OxLDL autoantibodies decreased, whereas apoB-IC levels increased after PCI, but both returned to baseline by 6 hours. Subsequently, IgM autoantibodies increased and peaked at 1 month and then returned to baseline, whereas IgG autoantibodies increased steadily over 6 months.

Conclusions—PCI results in acute plasma increases of Lp(a) and OxPL and results in short-term and long-term immunologic responses to OxLDL. OxPL that are released or generated during PCI are transferred to Lp(a), suggesting that Lp(a) may contribute acutely to a protective innate immune response. In settings of enhanced oxidative stress and chronically elevated Lp(a) levels, the atherogenicity of Lp(a) may stem from its capacity as a carrier of proinflammatory oxidation byproducts. (Circulation. 2004;109:3164-3170.)

Key Words: angioplasty • atherosclerosis • antibodies • lipoproteins

Oxidized low-density lipoprotein (OxLDL) is present in atherosclerotic lesions of animal models and humans and directly influences a multitude of atherogenic responses.1–4 In animals, OxLDL within plaques is preferentially depleted in response to regression/antioxidant diets.5–7 In humans, plaque specimens from carotid and coronary arteries are significantly enriched in OxLDL1,3 and become depleted in OxLDL after treatment with statins.8 In particular, unstable plaques appear to be preferentially enriched in OxLDL,9,10 and OxLDL in plasma has been shown to be associated with acute coronary syndromes9,11,12 and endothelial dysfunction.13,14

In the present study, we measured plasma levels of several OxLDL markers immediately before and serially up to 6 months after percutaneous coronary intervention (PCI) to evaluate the role of OxLDL in PCI.

Methods

Patients
The patient cohort was derived from a single-center, prospective study of 156 patients with stable angina undergoing elective, uncomplicated PCI.15,16 The study included men (77%); diabetics (18%); and patients with hypertension (44%), smoking (39%), and prior myocardial infarction (26%). Balloon angioplasty was per-
formed in 69% and stent placement in 31%. Blood samples were available from 141 patients, and 6-month angiographic follow-up was performed in 134 (95%) patients. Venous blood in EDTA was obtained before PCI, immediately after PCI; and 6 hours, 24 hours, 3 days, 1 week, and 1, 3, and 6 months after PCI.

Quantitative and qualitative (smooth, irregular, or ulcerated borders, concentric or eccentric appearance, calcification, thrombus) coronary angiographic measurements and American Heart Association/American College of Cardiology (AHA/ACC) lesion classification were performed according to previously described criteria.\textsuperscript{17} OxLDL markers and lipoprotein(a) [Lp(a)] levels were correlated with angiographic lesion characteristics.

In a control group of 50 patients who underwent diagnostic coronary angiography without any intervention, plasma samples were obtained immediately before and after angiography. The Human Subjects Protection Program at the University of California San Diego approved this study.

**Determination of OxLDL-E06 Levels, OxLDL Autoantibody Titers, and Apolipoprotein B-100–Immune Complexes**

Chemiluminescence ELISA was used to measure OxLDL markers. OxLDL-E06 is a measure of the content of oxidized phospholipids (OxPL) per apolipoprotein (apo) B-100 particle, using the murine monoclonal antibody E06, which specifically binds to the phosphorylcholine head group of oxidized but not native phospholipids (reviewed in Tsimikas et al\textsuperscript{11} and references therein). A 1:50 dilution of plasma in PBS is added to microtiter wells coated with the monoclonal antibody MB47, which specifically binds apoB-100 particles. Under these conditions, a saturating amount of apoB-100 is added to each well, and consequently, an equal number of apoB-100 particles are captured in each well for all assays. The content of OxPL per apoB-100 is then determined with biotinylated E06 as previously described.\textsuperscript{11} Plasma titers of IgG and IgM malondialdehyde (MDA-LDL) (1:200 plasma dilution) and copper-oxidized LDL (Cu-OxLDL (1:50 dilution) autoantibodies and apoB-100–immune complexes (apoB-IC; labeled LDL-IC previously)\textsuperscript{11} were measured as previously described.\textsuperscript{11} Internal controls consisting of high and low standard plasma samples were included on each microtiter plate to detect potential variations between microtiteration plates. Each sample was assayed in triplicate, and data are expressed as relative light units in 100 ms. The intra-assay coefficients of variation for all assays were 6% to 10%.

**Lp(a) Assay**

Plasma Lp(a) levels were measured by a novel chemiluminescent ELISA with the use of the murine monoclonal antibody LPA4, which was generated by immunizing mice with human Lp(a) and screening the hybridomas for antibodies that bound to a synthetic peptide of apo(a) with sequence TRNYCRNPDAEIRP. LPA4 does not cross-react with plasminogen. For this assay, MB47 (5 μg/mL) was plated on microtiter well plates to capture apoB-100 in human plasma [1:400 plasma dilution yielded a nonsaturating amount of Lp(a)] and Lp(a) detected with 50 μL of biotinylated LPA4. This assay correlated well (n=500, r=0.96, P<0.0001) with a commercially available Lp(a) assay (Diasonin).

**Determination of Binding of OxPL-E06 to Lp(a)**

To determine whether the OxPL-E06 epitope was bound to Lp(a) versus other apoB-100–containing lipoproteins, we added increasing amounts of antibody LPA4 [0- to 20-fold molar excess of LPA4:Lp(a) in the presence of 0.27 mmol/L EDTA, 0.02% sodium azide, and 25 μmol/L BHT] from 5 patients’ plasma, using samples from the pre-PCI, immediately post-PCI, 6-hour, 24-hour, and 6-month time points to immunoprecipitate Lp(a). After an overnight incubation at 4°C, the samples were centrifuged at 14,000 rpm for 30 minutes and 50-μL aliquots of the supernatants were added to MB47-coated plates and tested for the presence of Lp(a), OxPL, and apoB-100 by using biotinylated LPA4, E06, and goat anti-human apoB-100 (Biodesign International), respectively.

**Statistical Analysis**

Statistical analysis was performed with GraphPad InStat, version 3.02. For changes in OxLDL and Lp(a) levels in the PCI group, statistical analysis was performed with 1-way ANOVA with either the parametric Bonferroni multiple comparisons test or nonparametric Kruskal-Wallis tests. For comparison of angiographic characteristics to OxLDL and Lp(a) levels in the PCI group, an unpaired t test was performed at each time point; for differences in preangiography and postangiography samples in the control group, a paired t test was performed. The Mann-Whitney test was used for values that were not normally distributed. A Spearman correlation was used to determine relations between OxLDL markers and Lp(a). A value of P<0.05 was considered significant.

**TABLE 1. Quantitative and Qualitative Angiographic Characteristics of the Study Cohort**

<table>
<thead>
<tr>
<th>Coronary artery undergoing PCI, %</th>
<th>Before PCI</th>
<th>After PCI</th>
<th>At 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left anterior descending artery</td>
<td>56.7</td>
<td>22.4</td>
<td>20.9</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Quantitative angiographic characteristics, mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference diameter, mm</td>
</tr>
<tr>
<td>Lesion length, mm</td>
</tr>
<tr>
<td>Before PCI</td>
</tr>
<tr>
<td>After PCI</td>
</tr>
<tr>
<td>Minimal lumen diameter, mm</td>
</tr>
<tr>
<td>Before PCI</td>
</tr>
<tr>
<td>After PCI</td>
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<td>At 6 mo</td>
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<tr>
<th>Qualitative angiographic characteristics of target lesion</th>
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</thead>
<tbody>
<tr>
<td>AHA/ACC lesion classification, %</td>
</tr>
<tr>
<td>B1</td>
</tr>
<tr>
<td>B2</td>
</tr>
<tr>
<td>C</td>
</tr>
</tbody>
</table>

**Lesion surface, %**

| Smooth | 85.0 |
| Irregular | 9.0 |
| Ulcerated | 6.0 |

**Lesion appearance, %**

| Concentric | 69.9 |
| Eccentric  | 30.1 |
| Calcium, %  | 7.2 |
| Absent | 92.8 |
| Present | 7.2 |
| Thrombus, %  | 98.5 |
| Absent | 1.5 |
TABLE 3. Median (Range) Values of OxLDL Markers and Lp(a) in the Control Group

<table>
<thead>
<tr>
<th>Before</th>
<th>After</th>
<th>6 h</th>
<th>24 h</th>
<th>3 d</th>
<th>1 wk</th>
<th>1 mo</th>
<th>3 mo</th>
<th>6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a), mg/dL</td>
<td>16.0 (1.0–108.0)</td>
<td>16.0 (1.0–93.0)</td>
<td>16.0 (1.0–108.0)</td>
<td>16.0 (1.0–93.0)</td>
<td>16.0 (1.0–108.0)</td>
<td>16.0 (1.0–93.0)</td>
<td>16.0 (1.0–108.0)</td>
<td>16.0 (1.0–93.0)</td>
</tr>
<tr>
<td>OxLDL-E06</td>
<td>6215 (3331–75 833)</td>
<td>6475 (2870–68 202)</td>
<td>3267 (1618–67 323)</td>
<td>2641 (1220–13 328)</td>
<td>2641 (1220–13 328)</td>
<td>2641 (1220–13 328)</td>
<td>2641 (1220–13 328)</td>
<td>2641 (1220–13 328)</td>
</tr>
<tr>
<td>IC IgM</td>
<td>2702 (1618–6118)</td>
<td>2364 (278–6512)</td>
<td>2702 (1618–6118)</td>
<td>2364 (278–6512)</td>
<td>2702 (1618–6118)</td>
<td>2364 (278–6512)</td>
<td>2702 (1618–6118)</td>
<td>2364 (278–6512)</td>
</tr>
</tbody>
</table>

Units of OxLDL markers are in relative light units.

Results

Baseline, Postprocedural, and 6-Month Quantitative and Qualitative Angiographic Characteristics

Most lesions were type A and B1, smooth, concentric, and without significant calcification or thrombus (Table 1).

Absolute Baseline and Follow-Up Values of OxLDL Markers Lp(a)

Compared with pre-PCI levels, median post-PCI levels of OxLDL-E06 levels increased significantly [6177 to 7240 relative light units, P = 0.03] and promptly returned to baseline by 6 hours (Table 2). Similarly, median Lp(a) levels increased after PCI [7.0 to 9.9 mg/dL, P = 0.27] but not significantly and returned toward baseline by 6 hours. A strong correlation was noted between OxLDL-E06 and Lp(a) in the plasma samples obtained at all time points (r = 0.68, P < 0.0001, Figure 1). No significant differences were noted in other markers when evaluated as absolute levels. There were no significant differences in baseline levels between patients who had PCI and the angiography-only control group (n = 50) in all measures except that the patients who had PCI had a greater level of IgG-LDL immune complexes (P = 0.007) (Tables 2 and 3).

Changes in OxLDL-E06 and Lp(a) Levels

In this patient population, there was a wide baseline variation in the absolute values of Lp(a) and OxLDL at baseline that were not normally distributed. Therefore, we expressed each patient’s changes in OxLDL markers and Lp(a) in response to PCI as a percent change compared with the pre-PCI samples, and mean percent changes were calculated for all patients, which were generally normally distributed. For OxLDL-E06, there was a 36% mean percent increase after PCI compared with before PCI (P < 0.0001), and the post-PCI change was significantly different from all the other time points (P < 0.001, Figure 2). In parallel, Lp(a) levels increased 64% in the post-PCI time point, which was also statistically significant from all other time points measured (P < 0.001).

In contrast, in the angiography-only control group, no significant changes were noted in OxLDL-E06 or in Lp(a) levels between the preangiography and postangiography samples (Table 3).

Determination of Binding of Oxidized Phospholipid Epitopes to Lp(a)

The antibody LpA4 immunoprecipitated ≈95% of Lp(a) in each plasma sample at each time point, as expected (Figure 3A). Similar to Lp(a), the majority of E06 epitopes were also immunoprecipitated at all time points except in the immediate post-PCI time point, in which only ≈50% of the total E06 epitopes were associated with Lp(a) (Figure 3B), whereas the other 50%, because of the design of the assay, are by necessity on other apoB-containing lipoproteins not associated with Lp(a). However, by 6 hours and consistently for up to 6 months, nearly all the E06 epitopes are again associated with Lp(a).

Changes in OxLDL Autoantibodies and ApoB-IC

The mean percent change in Cu-OxLDL and MDA-LDL IgM titers decreased significantly in the post-PCI sample (P < 0.0001 for both) but returned to baseline by 6 hours. Subsequently, titers increased, peaked at 1 month, and then returned toward baseline by 6 months (Figure 4, A and B).
Cu-OxLDL ($P<0.016$) and MDA-LDL ($P<0.0001$) IgG titers also initially decreased in the post-PCI sample but returned to baseline by 6 hours. Over the ensuing 6 months, they demonstrated a modest but persistent increase (Figure 4, C and D). No changes were noted in these markers in the control group.

There was a reciprocal increase in IgM apoB-IC ($P=0.021$ by ANOVA) and a trend toward an increase in IgG apoB-IC ($P=0.099$ by ANOVA, Figure 5) after PCI. Interestingly, the levels returned to baseline by 24 hours and then peaked at 1 to 3 months, in parallel with the elevation in OxLDL autoantibody titers. By 6 months, the apoB-IC levels had returned to baseline. No changes were noted in these markers in the control group.

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Relation of Angiographic Variables to OxLDL Markers

There were no significant associations between OxLDL markers or Lp(a) and angiographic characteristics, nor were there significant associations in patients undergoing balloon angioplasty versus stent placement (data not shown).

Clinical Outcomes

Two patients (1 each in the balloon and stent groups) had subacute vessel occlusion at day 4 and had a myocardial infarction. One patient died suddenly at day 7. Six-month follow-up showed only 1 non–target vessel revascularization and 35 target vessel revascularizations (33 PCI, 2 CABG) related to restenosis. No significant differences in OxLDL markers were noted between patients having nonrestenotic events and the entire cohort.

Discussion

This study demonstrates for the first time that PCI results in acute plasma elevations of both OxLDL-E06 and Lp(a). Plasma oxidized phospholipid epitopes detected by E06 (OxLDL-E06) were predominantly physically associated with Lp(a) in all samples tested except in the immediate post-PCI sample, in which they were bound to both non–Lp(a)-containing apoB-100 particles and Lp(a) but transferred to Lp(a) particles within 6 hours. In addition, a strong correlation was confirmed between OxLDL-E06 and Lp(a). This may have pathophysiological consequences, as such OxPL have been shown to have a variety of proinflammatory properties. In addition, the long-term OxLDL antigen/autoantibody responses were consistent with OxLDL acting as an immunogen in patients who were already sensitized by previous exposure. These observations support the hypothesis that OxPL are present in disrupted plaques and are released into the circulation by PCI, where they are bound by apoB-containing lipoproteins, and preferentially by Lp(a). Furthermore, they define a novel relation between OxPL and Lp(a) and suggest new insights into the role of Lp(a) in normal physiology as well as in atherogenesis.

What is the cause of the rise in OxPL and Lp(a) after PCI? One possibility is that both OxPL and Lp(a) are derived from disrupted plaque contents, inasmuch as both have been previously documented to be enriched in atherosclerotic lesions in vivo.

Figure 2. Relative changes (mean percent change from pre-PCI levels) of OxLDL-E06 (A) and Lp(a) (B) after PCI. *$P<0.016$ compared with other time points.

Figure 3. Levels of Lp(a) (A), OxLDL-E06 (B), and apoB-100 (C) in plasma after in vitro precipitation of Lp(a) with increasing doses of antibody LP4A4. Data represent mean values of samples obtained from 5 patients at indicated time points before and after PCI. Patients studied had the highest values of Lp(a) and OxLDL-E06 in the post-PCI sample.
eral studies have clearly documented that PCI results in plaque compression, redistribution, or disruption, and intimal and medial dissection; that emptied plaque cavities are noted in patients with spontaneous plaque rupture; and that placing stents in patients with unstable angina leads to a marked reduction in plaque burden, suggesting compression and embolization of plaque material.21

Another possibility for the rise in plasma content of OxPL but probably not Lp(a) is a consequence of transient oxidative stress secondary to ischemia/reperfusion occurring during PCI causing increased lipid peroxides. Buffon et al22 observed transient (<15 minutes’ duration) elevation of free lipid peroxides in the coronary sinus during balloon occlusion of the left anterior descending coronary artery. However, in contrast to our study, in which OxPL were present in the systemic circulation, lipid peroxides were not present in the systemic circulation or after PCI of the right coronary artery. Although the E06 assay does not detect lipid peroxides, it is possible that lipid peroxides generated secondary to such ischemia/reperfusion may oxidize phospholipids in the vessel wall or even in plasma, which would then be subsequently detected as OxPL (eg, E06 reactivity) bound to LDL or Lp(a) in plasma. Further studies are needed to explore this possibility.

Another possibility for the acute increases in Lp(a) is rapid synthesis of apo(a) by the liver (possibly by cytokines upregulated during PCI), where it may bind to LDL, creating Lp(a) particles. Perhaps apo(a) was released from a pre-formed hepatic pool. For example, it is possible that release of OxPL from the plaque upregulates liver apo(a) synthesis, as the apo(a) gene has an IL-6 response element leading to enhanced transcription,23 similar to the effect of cytokines that upregulate C-reactive protein synthesis. Patients with the highest baseline Lp(a) levels had the greatest absolute increases in Lp(a) after PCI. The mean Lp(a) levels rose on average by \( \approx 8 \text{ mg/dL} \) (from 21.7 to 29.8 mg/dL) before PCI to after PCI. Assuming a 6-L plasma volume, this suggests that the absolute plasma Lp(a) content, on average, was increased by \( \approx 500 \text{ mg} \) during the time it takes to perform PCI. However, despite the fact that Lp(a) correlates with angiographic disease and has a predilection for and is enriched in unstable atherosclerotic plaques,20,24 it seems unlikely that this amount of Lp(a) is derived from the site of plaque disruption alone.

What are the clinical consequences of the increased plasma levels of these substances during PCI? In the present study, patients with procedural complications were excluded by definition, and nonrestenotic major adverse cardiac events were exceedingly low in these patients with stable angina. However, data from experimental and human13 studies have suggested that OxLDL and in particular OxLDL-E06,14 as well as Lp(a), contain vasoactive moieties.25 It is possible that release of such vasoactive substances during PCI may lead to vasoconstriction of the microvasculature and no-reflow phenomenon.
The association between OxLDL-E06 and Lp(a) has been documented only recently, and a potential pathophysiological link was provided by demonstrating binding of proinflammatory OxPL by Lp(a) and even covalent adduct formation with apo(a). We have recently shown that kringle V of apo(a) covalently binds 2 moles of OxPL detected by antibody E06 and that this portion of apo(a) induced IL-8 production by macrophages. We recently demonstrated that both OxLDL-E06 and Lp(a) rise concurrently after acute coronary syndromes, but unlike the present study, in which levels increased only after PCI in otherwise uncomplicated procedures, levels remained elevated up to 3 to 6 months. In the present study, we documented for the first time a transient disassociation of OxLDL-E06 and Lp(a) in the post-PCI samples, suggesting that these two compounds are independently generated to some extent but later reassociate. We have suggested that Lp(a), compared with LDL, preferentially binds such OxPL, and in vitro transfer studies suggest this hypothesis (Tsimikas, Witztum, unpublished observations). Thus, we suggest that Lp(a) acts as a “sink” for such OxPL in vivo, providing a mechanism for their transport and potentially even their degradation, as it has been reported that Lp(a) contains a high content of platelet-activating factor acetylhydrolase, which would destroy the proinflammatory properties of OxPL by removing the oxidized fatty acid. From these data, we hypothesize that a potential physiological role for Lp(a) may be to protect organisms from oxidative stress. In this way, it may be part of the innate immune response, similar to C-reactive protein, which has also been shown to bind OxPL. This would suggest that low levels of Lp(a) may actually be beneficial. On the other hand, its atherogenicity may rise from the fact that when plasma levels of Lp(a) are elevated, an enhanced number of Lp(a) particles would enter the vessel wall, where Lp(a) is preferentially bound to the extracellular matrix, and, with its enhanced content of OxPL, Lp(a) would have profound proinflammatory properties.

The long-term immunogenic responses to the released OxLDL are unique observations and confirm that OxLDL plays a role in initiating immune responses in atherogenesis. The immediate decline in free autoantibody levels probably represents acute immune complex formation, as apoB-IC rose simultaneously. If one assumes that the released products of OxLDL, such as OxPL measured in our assay, are proinflammatory and promote endothelial dysfunction, then the trapping of these epitopes by such autoantibodies may be beneficial. The long-term increase in IgG and IgM autoantibodies presumably reflects an anamnestic response or synthesis of totally new species of OxLDL antibodies and is consistent with acute presentation of OxLDL to a previously sensitized immune system. Whether these long-term responses are protective (or even adverse) is not clear, although immunization of animals with OxLDL or pneumococcal vaccine, which results in increased OxLDL autoantibodies, provides protection against atherosclerosis. However, additional immune mechanisms are probably involved in this protection, and further research is needed to determine the role of OxLDL autoantibodies in human disease.

Limitations of this study include the fact that direct capture and analysis of embolized debris for OxLDL and Lp(a) were not performed. Thus, the immediate source of increased levels of OxLDL-E06 and Lp(a) in plasma and the direct underlying mechanisms responsible for these changes were not investigated. In addition, the patient cohort was composed only of patients with stable angina undergoing elective, uncomplicated procedures with fairly uniform and simple lesion characteristics; therefore, it is not clear if patients with complications during PCI would have similar changes.

In conclusion, PCI results in acute elevations of OxLDL-E06 and Lp(a) and long-term OxLDL/autoantibody responses. These observations provide impetus for further studies into the role of OxLDL in plaque disruption, ischemia/reperfusion, and coronary blood flow during PCI and the physiological role of Lp(a) and its potential atherogenicity.

Acknowledgments

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References


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