Effect of Cardiopulmonary Bypass and Heparin on Plasma Levels of Lp(a) and Apo(a) Fragments


Abstract—Fragments of apolipoprotein(a) [apo(a)], the distinctive glycoprotein of lipoprotein(a) [Lp(a)], are present in human plasma and urine and have been implicated in the development of atherosclerosis. The mechanism responsible for the generation of apo(a) fragments in vivo is poorly understood. In this study, we examined the plasma levels of Lp(a) and apo(a) fragments [or free apo(a)] and urinary apo(a) in 15 subjects who underwent cardiac surgery necessitating cardiopulmonary bypass. We also measured the plasma concentration and activity of polymorphonuclear elastase, an Lp(a)-cleaving enzyme in vitro, and plasma levels of C-reactive protein. Despite a marked activation of polymorphonuclear cells and a pronounced inflammatory response, as documented by an 8-fold and a 35-fold increase in plasma levels of polymorphonuclear elastase and C-reactive protein, respectively, the proportion of plasma free apo(a) to Lp(a) and urinary excretion of apo(a) remained unchanged over a 7-day period after surgery, and polymorphonuclear elastase activity remained undetectable in plasma. No fragmentation of apo(a) was observed ex vivo in plasma samples collected before and after surgery. These data indicate that in this model, apo(a) is not fragmented in plasma and are consistent with the hypothesis that apo(a) fragments result from a constitutively active tissue mechanism that is not modified by cardiac surgery with cardiopulmonary bypass. (Arterioscler Thromb Vasc Biol. 1999;19:1060-1065.)

Key Words: apolipoprotein(a) ■ atherosclerosis ■ elastase ■ heparin ■ lipoprotein(a)

A polipoprotein(a) [apo(a)] is a glycoprotein of unknown function that is associated with the premature development of atherosclerosis. Full-length apo(a) and fragments of apo(a) have been identified in human plasma. More than 99% of full-length apo(a) is attached to apolipoprotein B-100 (apoB) of LDL and circulates as part of lipoprotein(a) [Lp(a)]. Plasma Lp(a) levels vary widely between individuals and are largely determined by sequences at or close to the apo(a) locus. The apo(a) gene is homologous to the plasminogen gene. Plasminogen contains 5 kringles (K) and the protease domain. In contrast, the apo(a) gene is highly polymorphic due to a variable number of tandemly repeated copies of a motif resembling kringle 4 (K4) of plasminogen. In apo(a), the array of apo(a)-K4 repeats is followed by 1 K5 unit and the protease domain, which is functionally inactive. K4-containing fragments from the N-terminus of apo(a) are present in human plasma and urine. In plasma, the percentage of apo(a) fragments to Lp(a) is correlated inversely with plasma Lp(a) levels.

The mechanism by which apo(a)/Lp(a) is atherogenic is not known. Identification of apo(a) fragments in atherosclerotic plaques has raised the hypothesis that fragments of apo(a) may contribute to the atherogenicity of Lp(a). As a consequence, interest has been generated regarding the molecular mechanism responsible for the production of apo(a) fragments. Apo(a) fragments do not appear to be secreted by hepatocytes but are more likely products of extracellular cleavage of apo(a)/Lp(a). However, the enzyme(s) responsible for this reaction and the site in which it takes place are not known. Recent in vitro studies by Scanu's group have identified polymorphonuclear (PMN) elastase as an apo(a)/Lp(a)-cleaving enzyme. Indeed, cleavage of apo(a)/Lp(a) by PMN elastase at various interkringle sites generates N-terminus fragments of apo(a) similar in size to those identified in human plasma and “mini-Lp(a).” Mini-Lp(a), which contains the C-terminus of the tandem array of K4 repeats, K5, and the protease domain of apo(a) attached to apoB, is not detected in plasma, suggesting that mini-Lp(a), which has maintained its ability to bind fibrin and heparin, is retained within the extracellular matrix whereas N-terminus fragments of apo(a) are released into the circulation. Whether this scenario is operative in vivo is not known. Elucidation of the mechanism responsible for the generation of apo(a) fragments in vivo is hampered by the unusual species distribution of apo(a), which is restricted to humans, Old World monkeys, and hedgehogs. Finally, apo(a) fragments are not present in plasma from transgenic mice expressing human apo(a).
To better understand the mechanism responsible for the generation of apo(a) fragments in vivo in humans, we measured serially the plasma levels of Lp(a) and apo(a) fragments (or free apo(a)) and urinary apo(a) in 15 subjects who underwent elective cardiac surgery with cardiopulmonary bypass (CPB). This type of surgery was chosen as a “model” because this well-standardized and well-documented procedure is accompanied by a major, acute, and transient inflammatory response that includes activation of PMN cells and the release into the circulation of large amounts of PMN elastase.20 PMN elastase has been implicated in acute lung injury and microvascular permeability after CPB.21,22 Next, the effect of surgery with CPB on plasma Lp(a) levels remains an unresolved issue, with some investigators reporting increased23 or unchanged24,25 plasma Lp(a) levels after this procedure. Finally, we took advantage of this model to examine whether a large bolus of heparin has the ability to release tissue-bound Lp(a) into the circulation. As for CPB, the effect of heparin on plasma Lp(a) levels has previously been examined, but conflicting results have been reported.19,26,27

Methods

Subjects and Study Design

Participants to this study were recruited from those patients who underwent elective cardiac surgery necessitating CPB. Individuals with plasma creatinine levels >110 µmol/L; those who had suffered an acute illness or myocardial infarction or had undergone major surgery within 4 weeks preceding CPB; and those who presented with major abnormalities in lipid metabolism were excluded from the study. After median sternotomy, a bolus of heparin was injected (300 IU/kg body weight), and the CPB circuit was installed. CPB was performed with disposable membrane oxygenators and was primed with Ringer’s lactate buffer, 5000 IU/L of heparin, and 10^6 IU aprotinin. Subjects were followed up for a 1-week period after surgery.

A total of 5 mL of blood was collected at 9 different time points from the intravenous line after it had been flushed. Blood was collected 1 hour before surgery (T1); immediately before heparin administration (T2); 15 minutes after heparin administration (T3); 60 minutes after initiation of CPB (T4); at completion of surgery (T5); and at 4, 24, and 48 hours and 7 days after surgery (T6 through T9, respectively). Urine samples were collected at times T2 and T5 through T9. Blood was collected in EDTA-containing tubes and maintained on ice for a maximum of 2 hours before centrifugation. An exception was T6, for which blood samples were stored for 12 hours at 4°C before centrifugation. Plasma was isolated and aliquots were stored at −80°C. All assays were performed on freshly thawed plasma samples except for cholesterol and triglyceride levels, which were assayed in plasma samples that had been thawed and refrozen once. Additional plasma and serum samples were collected from 4 severely ill subjects who had been admitted to the surgical intensive care unit of the hospital. The protocol was approved by the local ethics committee, and all participants gave their informed consent.

Laboratory Methods

Plasma levels of Lp(a) were quantified by an ELISA.28 This assay uses IgG-a6 as a capture mouse monoclonal antibody (Mab) and IgG-a40 as a detecting Mab. IgG-a6 and IgG-a40 recognize epitopes in the N-terminus and the C-terminus of apo(a), respectively. Plasma free apo(a) was separated from Lp(a) by the heparin-Sepharose chromatography method, as described.8 Free apo(a) was assayed in the nonretained fraction by ELISA with IgG-a6 as the capture antibody and IgG-a5, an Mab directed against the N-terminus of apo(a), as the detecting antibody. In addition, apo(a) in untreated plasma and in the heparin-unbound fraction was examined by immunoblot analysis by 5% SDS–polyacrylamide gel electrophoresis, as described.29 The size of the apo(a) isoforms in plasma was determined as described.30 Apo(a) in urine was quantified using the same ELISA as for free apo(a).11

Plasma levels of PMN elastase were measured using a homogeneous immunoturbidimetric assay (PMN elastase, Ecoline Merck) on a Cobas Mira Plus analyzer (Roche) according to the manufacturer’s instructions. The interassay CV was <4% for values <130 µg/L. Normal values for this assay were 29 to 86 µg/L, with a detection level of 9 µg/L. Measurement of the activity of PMN elastase in plasma was performed using a colorimetric assay.31 This assay uses 3-carboxypropionyl-Ala-Ala-Val-4-nitroaniline as a specific substrate for PMN elastase and detects generation of the yellow product 4-nitroanilide. Control for the assay was performed by comparing the concentration of PMN elastase and the elastolytic activity in the supernatant after stimulation of purified PMN cells with fMet-Leu-Phe (1 µmol/L) and cytochalasin B (5 µg/mL). In this assay, the activity of 200 µg of PMN elastase corresponded to the digestion of 1 µmol/min of specific substrate.

Plasma levels of creatine kinase (CK), creatinine, and albumin were assayed according to the manufacturer’s instructions on a Hitachi 717 selective analyzer (Boehringer Mannheim). Creatinine in urine was measured similarly on a Hitachi 704 analyzer. C-reactive protein (CRP) was assayed using a homogeneous immunoturbidimetric assay (Dako) on a Hitachi 717 analyzer. The interassay CV was 3% for values between 30 and 100 mg/L. Reference values for plasma CRP levels were <10 mg/L. Plasma concentrations of cholesterol and triglycerides were determined using the Unimate5-CHOL and Unimate7-TRIG kits, respectively (Roche). HDL cholesterol levels were measured using the same kit after precipitation of apoB-containing lipoproteins by the phosphotungstate-MgCl2 method (Boehringer-Mannheim). The LDL cholesterol fraction was calculated using the Friedewald formula. Statistical analysis was performed using the STATA package (Stata Corp, College Station, Tex). One-way ANOVA was used to test for variance during the study period. In case of variance, the analysis was completed by paired t tests [or Wilcoxon rank-sum test in the case of plasma Lp(a) levels] to detect significant changes from baseline.

Results

A total of 9 males and 6 females aged 45 to 72 years participated in the study. Two subjects were on lipid-lowering therapy, whereas 4 individuals were diabetics. Ten subjects underwent CPB for coronary artery bypass grafting (CABG), 4 for valve replacement, and 1 for both valve replacement and CABG on 1 vessel. None of the subjects had any acute condition, renal insufficiency, or major lipid abnormalities. No major complication was observed in the perioperative or postoperative period. Baseline plasma Lp(a) levels ranged from 0.3 to 79.4 mg/dL (median, 11.1 mg/dL). The size of the apo(a) isoforms ranged from 20 to 36 K4 repeats, and an inverse relationship was apparent between plasma Lp(a) levels and the size of the apo(a) isoforms in plasma.

Initiation of CPB was associated with an abrupt reduction in hematocrit [from 0.43±0.02 at baseline to 0.33±0.01 (mean±SEM) 4 hours after completion of surgery]; (Table). Changes in hematocrit were paralleled by reductions in plasma levels of albumin and total, HDL, and LDL cholesterol (from 3.0±0.2 mmol/L to 1.8±0.2 mmol/L). These acute changes were mainly due to hemodilution induced by the large volume of Ringer’s lactate buffer used to prime the CPB circuit. Cardiac surgery with CPB was associated with a 35-fold increase in plasma CRP levels (from 6±2 mg/L at baseline to 209±23 mg/L 48 hours after surgery, P<0.01) that tended to normalize 1 week after surgery (48±5 mg/L). Changes in CRP levels were paralleled by changes in CK levels (from 72±11 to 390±124 mg/L, P<0.01) and leuko-
Biological Variables Before, During, and After CPB in 15 Individuals

<table>
<thead>
<tr>
<th>T1: Baseline</th>
<th>T2: Before Heparin</th>
<th>T3: After Heparin</th>
<th>T4: During CPB</th>
<th>T5: 0 h</th>
<th>T6: 4 h</th>
<th>T7: 24 h</th>
<th>T8: 48 h</th>
<th>T9: 7 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>0.43±0.02</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Leukocytes, 10^6/L</td>
<td>7.7±0.7</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>12.2±1.2</td>
<td>12.1±0.9</td>
<td>13.2±0.8</td>
<td>8.2±0.6*</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>80±3</td>
<td>76±8†</td>
<td>75±7†</td>
<td>76±7†</td>
<td>76±9†</td>
<td>78±13†</td>
<td>80±5</td>
<td>80±4</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>41.5±0.8</td>
<td>38.4±1.8</td>
<td>32.3±2.0</td>
<td>26.3±0.6</td>
<td>29.3±1.1</td>
<td>29.8±1.3</td>
<td>33.1±0.9</td>
<td>32.4±0.8</td>
</tr>
<tr>
<td>CK, U/L</td>
<td>72±11</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>439±79</td>
<td>438±60</td>
<td>390±124</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>6.0±2.0</td>
<td>4.7±3.1</td>
<td>4.5±2.2</td>
<td>3.7±2.0</td>
<td>3.4±2.0</td>
<td>18.8±12.8</td>
<td>117±13</td>
<td>209±23</td>
</tr>
<tr>
<td>PMN elastase, μg/L</td>
<td>37±4</td>
<td>41±3</td>
<td>33±4</td>
<td>107±15</td>
<td>269±27</td>
<td>180±20</td>
<td>110±8</td>
<td>125±12</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.8±0.2</td>
<td>4.4±0.3</td>
<td>...</td>
<td>2.9±0.1</td>
<td>3.1±0.2</td>
<td>2.6±0.2</td>
<td>2.9±0.1</td>
<td>4.1±0.2*</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.1±0.1</td>
<td>1.0±0.1</td>
<td>...</td>
<td>0.6±0.1</td>
<td>0.7±0.1</td>
<td>0.8±0.1</td>
<td>0.8±0.1</td>
<td>0.9±0.1*</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.8±0.2</td>
<td>1.6±0.2</td>
<td>...</td>
<td>0.8±0.1</td>
<td>1.4±0.2</td>
<td>1.3±0.1</td>
<td>2.0±0.2</td>
<td>2.2±0.1*</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.0±0.2</td>
<td>2.8±0.3</td>
<td>...</td>
<td>2.0±0.1</td>
<td>1.8±0.2</td>
<td>1.2±0.1</td>
<td>1.2±0.1</td>
<td>2.1±0.2*</td>
</tr>
<tr>
<td>Lp(a), mg/dL, median</td>
<td>11.1</td>
<td>11.4</td>
<td>10.9</td>
<td>7.8</td>
<td>11.9</td>
<td>9.5</td>
<td>11.2</td>
<td>9.3</td>
</tr>
<tr>
<td>Lp(a), mg/dL</td>
<td>26.9±6.1</td>
<td>26.3±6.3</td>
<td>24.5±7.4‡</td>
<td>14.9±3.6</td>
<td>17.2±3.9</td>
<td>14.7±3.4</td>
<td>13.9±3.2</td>
<td>12.7±3.0</td>
</tr>
<tr>
<td>Lp(a)/LDL-C, % of T1§</td>
<td>100</td>
<td>111±10</td>
<td>93±4</td>
<td>99±8</td>
<td>150±12</td>
<td>130±10</td>
<td>154±14*</td>
<td></td>
</tr>
<tr>
<td>Free apo(a)/Lp(a)×100§</td>
<td>2.8±0.4</td>
<td>3.2±0.5</td>
<td>(7.7±1.8)</td>
<td>(6.4±0.9)</td>
<td>3.2±0.5</td>
<td>3.0±0.5</td>
<td>3.0±0.4</td>
<td>3.1±0.5</td>
</tr>
</tbody>
</table>

All values are mean±SEM, except where noted otherwise.

*P<0.01 by ANOVA.
†Mean±SEM of only 6 samples.
‡n=12. Three subjects who had CPB installed before blood collection at time T3 were not included.
§n=14. One subject with a baseline plasma Lp(a) level of 0.3 mg/dL was excluded from the analysis because of uninterpretable relative changes.
¶Data not included in the statistical analysis because of incomplete precipitation of Lp(a) in the presence of heparin in plasma during CPB.

Cyte counts (from 7.7±0.7 to 13.2±0.8×10^6/L, P<0.01). In addition, plasma levels of immunoreactive PMN elastase rose from 37±4 to 269±27 μg/L (P<0.01) at completion of the surgical procedure and decreased progressively in the postsurgical period to 66±1 mg/L after 1 week. These observations reflect the importance of the acute and transient inflammatory response generated by surgery with CPB.

The individual profiles of plasma Lp(a) levels during the study period are illustrated in Figure 1 (upper panel). Plasma levels of in the presence of heparin in plasma, as assessed by immunoblot analysis of apo(a) in untreated plasma and in the heparin-unbound fraction (Figure 2). In the postsurgical period, plasma levels of free apo(a) closely paralleled plasma Lp(a) levels (Figure 1, second panel), with the lowest concentrations at 48 hours after surgery (0.35±0.06 versus 0.70±0.12 mg/dL at baseline, P<0.05). Apart from the values obtained during CPB, the pattern of apo(a) fragments (Figure 2) and the ratio of free apo(a) to Lp(a) remained remarkably stable throughout the study period (2.8±0.4% at baseline, 3.0±0.5% 4 hours after surgery, and 3.1±0.5% at 48 hours after surgery, the Table), with a slight reduction to 2.0±0.3% by day 7 (P=NS).

It is conceivable that an acceleration in apo(a) fragmentation went unnoticed due to the rapid and efficient excretion of apo(a) fragments into the urine. To address this question, urine was collected at baseline (T2) and in the postsurgical period (T5 to T9), and urinary apo(a) was quantified. The concentration of urinary apo(a) decreased from 0.17±0.05 μg/mL at baseline to 0.08±0.02 μg/mL at completion of the surgery and increased progressively in the postsurgical period (Figure 1, third panel). Urinary levels of apo(a) and creatinine (open triangles) evolved in parallel, indicating that the changes in urinary apo(a) levels were mainly due to variations in urinary output. To circumvent the problem of variable diuresis, we normalized the concentration of urinary apo(a) with respect to urine creatinine levels. At baseline, urinary excretion of apo(a) averaged 29.7±4.9 μg/mmol of creatinine and remained relatively stable throughout the study period (Figure 1, lower panel). Taken together, these observations indicated that even if fragmentation of apo(a) had been accelerated by CPB, the apo(a) fragments that were generated did not accumulate in the plasma or urine.

To gain further insight into the generation of apo(a) fragments, we performed ex vivo experiments on plasma samples collected before and after surgery from 4 subjects with baseline plasma Lp(a) levels ranging from 6.4 to 25.7 mg/dL. Plasma samples were incubated at 37°C for 1 or 4 hours, and plasma levels of Lp(a) and free apo(a) were quantified. In plasma samples collected before surgery, the proportion of free apo(a) to Lp(a) averaged 1.7±0.4% before incubation, 2.1±0.8% after a 1-hour, and 1.7±0.3% after a
4-hr incubation at 37°C. The respective values for plasma samples collected after CPB (T5) were 1.6 ± 0.2%, 1.4 ± 0.3%, and 1.4 ± 0.4%. These data indicate that fragmentation of apo(a) is unlikely to happen in plasma, even after a major insult like CPB. The absence of apo(a) fragmentation in plasma prompted us to examine the activity of PMN elastase in plasma. No PMN elastase activity was detected in plasma samples collected at times T1, T5, T6, and T9, indicating that PMN-derived elastase in plasma is biologically inactive.

Next, we examined whether a major insult other than CPB would be accompanied by apo(a) fragmentation in plasma. Plasma and serum samples were collected from 4 severely ill subjects admitted to the surgical intensive care unit of the hospital. One subject had acute respiratory distress syndrome, the second had polytrauma, and the remaining 2 subjects had extensive burns (>25% of body surface area). Plasma levels of Lp(a) ranged from 5.0 to 25 mg/dL, CRP from 164 to 424 mg/L, and leukocyte counts from 10^9/L to 17.4 ± 10^9/L. Individual plasma elastase concentrations were 542, 363, 131, and 179 mg/L; however, no significant PMN elastase activity was detected in these plasma samples. No generation of apo(a) fragments was observed in plasma samples after 1 (3.0 ± 0.5% versus 3.0 ± 0.4% before incubation) and 4 (3.3 ± 0.4%) hours of incubation at 37°C, indicating that, as is the case for CPB, fragmentation of apo(a) in plasma is unlikely to occur in these situations.

**Discussion**

The presence in healthy volunteers of apo(a) fragments in plasma and urine, coupled with the observation that apo(a) fragments are not produced by hepatocytes in monkeys, indicates the existence of an extracellular mechanism responsible for the cleavage of Lp(a)/apo(a). The present study was designed to evaluate whether this cleavage mechanism is accelerated when humans are exposed to a major insult and whether this mechanism is operative in plasma. Our data show that the proportion of plasma free apo(a) to Lp(a) and the urinary excretion of apo(a) remained unchanged after
surgery with CPB, despite a marked inflammatory response. In addition, no increase in plasma PMN elastase activity was noticed during CPB, and no fragmentation of apo(a) in plasma was observed ex vivo.

To our knowledge, this is the first study to perform serial measurements of plasma levels of free apo(a) and urinary apo(a) in humans. The stability of the proportions of plasma levels of free apo(a) to Lp(a) was unexpected, given the marked inflammatory response generated by CPB. Several mechanisms can be proposed to account for this observation. It is conceivable that apo(a) fragmentation was accelerated in tissues after CPB but that this phenomenon remained unnoticed owing to the retention of apo(a) fragments within the extravascular compartment or to a rapid clearance of these fragments. This latter hypothesis, however, is unlikely, because no accumulation of apo(a) fragments was observed in urine. More likely, our data indicate that the tissue mechanism responsible for the generation of apo(a) fragments is unaffected by CPB and that fragmentation of apo(a) does not occur in plasma. The absence of apo(a) fragmentation in plasma, despite the large amount of PMN elastase released after CPB, is probably due to the presence of excess protease inhibitors like α1-antitrypsin. However, we cannot formally rule out the possibility that aprotinin, which was present in the CPB priming buffer, may have inhibited the fragmentation of apo(a), even when administered at minimal doses, as was the case here. Such a hypothesis, however, is unlikely. First, no reduction in the plasma free apo(a) to Lp(a) ratio was observed during CPB, indicating that cleavage of apo(a)/Lp(a) is not aprotinin-sensitive. Next, no apo(a) fragmentation was observed in plasma from 4 severely ill subjects who had not received any protease inhibitors.

Our data also show that Lp(a), when attached to tissues, cannot be displaced by a large bolus of heparin. This finding is in agreement with those of other investigators19 who had not received any protease inhibitors.

In addition, no increase in plasma PMN elastase activity was noticed during CPB, and no fragmentation of apo(a) in plasma was observed ex vivo. To our knowledge, this is the first study to perform serial measurements of plasma levels of free apo(a) and urinary apo(a) in humans. The stability of the proportions of plasma levels of free apo(a) to Lp(a) was unexpected, given the marked inflammatory response generated by CPB. Several mechanisms can be proposed to account for this observation. It is conceivable that apo(a) fragmentation was accelerated in tissues after CPB but that this phenomenon remained unnoticed owing to the retention of apo(a) fragments within the extravascular compartment or to a rapid clearance of these fragments. This latter hypothesis, however, is unlikely, because no accumulation of apo(a) fragments was observed in urine. More likely, our data indicate that the tissue mechanism responsible for the generation of apo(a) fragments is unaffected by CPB and that fragmentation of apo(a) does not occur in plasma. The absence of apo(a) fragmentation in plasma, despite the large amount of PMN elastase released after CPB, is probably due to the presence of excess protease inhibitors like α1-antitrypsin. However, we cannot formally rule out the possibility that aprotinin, which was present in the CPB priming buffer, may have inhibited the fragmentation of apo(a), even when administered at minimal doses, as was the case here. Such a hypothesis, however, is unlikely. First, no reduction in the plasma free apo(a) to Lp(a) ratio was observed during CPB, indicating that cleavage of apo(a)/Lp(a) is not aprotinin-sensitive. Next, no apo(a) fragmentation was observed in plasma from 4 severely ill subjects who had not received any protease inhibitors.

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 Plasma levels of Lp(a) and LDL cholesterol evolved in parallel during the surgical procedure. However, in the post-surgical period, plasma Lp(a) levels returned to values above baseline at day 7, at a time when plasma LDL cholesterol levels were still ≈30% below baseline. The evolution of plasma Lp(a) levels as observed here was similar to the one previously reported after CPB,25 other surgical interventions,34 after myocardial infarction,34–36 or after administration of bisphosphonates.37 Taken together, these observations are consistent with the concept that Lp(a) reacts to inflammation, even when the Lp(a) response is delayed compared with the typical acute-phase reactant CRP.34,38

At the present time, whether apo(a) fragments have a biological function in plasma or in urine and whether they participate in the development of atherosclerosis remain to be established. If the role of apo(a) fragments in the development of atherosclerosis is once confirmed, identification of the mechanism responsible for their generation or their excretion may potentially unravel novel targets in the prevention and the treatment of this disease.

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