Elevated Serum Lipoprotein(a) Level Is an Independent Marker of Severity of Thoracic Aortic Atherosclerosis*

Marcel Peltier, MD; Michèle C. Iannetta Peltier, MD; Maurice E. Sarano, MD; Jean-Philippe M. Lesbre, MD; Jean-Laurent Colas, MD; and Christophe M. Tribouilloy, MD, PhD

Study objective: Lipoprotein(a) (Lp[a]) level is a risk factor for ischemic heart disease, cerebrovascular disease, and peripheral vascular disease. However, few data are available concerning the relationship between Lp(a) level and severity of thoracic aortic atherosclerosis. We hypothesized in this transesophageal echocardiography (TEE) study that Lp(a) level is a marker of severity of thoracic aortic atherosclerosis.

Design: Cross-sectional study.

Setting: University hospital.

Patients: Risk factors, coronary angiographic features, and TEE findings were analyzed prospectively in 119 patients with valvular disease.

Measurements and results: The following risk factors were recorded: age, gender, hypertension, smoking, lipid parameters, diabetes, body mass index, and family history of coronary artery disease. Serum levels of Lp(a) were measured for each patient. By univariate analysis, age, diabetes, hypertension, smoking, Lp(a), total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels were significant predictors of thoracic aortic atherosclerosis. There was a positive and significant correlation between the Lp(a) levels and the score of severity of thoracic aortic atherosclerosis (p < 0.0001). Multivariate regression analysis revealed that Lp(a) was an independent predictor of severity of thoracic aortic atherosclerosis (p = 0.0001).

Conclusion: This prospective study indicates that serum Lp(a) level is an independent marker of severity of thoracic aortic atherosclerosis detected by multiplane TEE. These findings emphasize the role of Lp(a) as a marker of atherosclerotic lesions in the major arterial locations.

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Key words: atherosclerotic plaque; lipoprotein A; thoracic aorta; transesophageal echocardiography

Abbreviations: CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein (a); TAAP = thoracic aortic atherosclerotic plaque; TEE = transesophageal echocardiography

The association between conventional blood lipid parameters and apolipoproteins in the development and progression of cardiovascular atherosclerotic disease is widely accepted. Elevated serum lipoprotein(a) (Lp[a]) is an independent predictor of coronary artery disease (CAD) and myocardial infarction, intermittent claudication, cerebrovascular disease, and peripheral vascular disease. In addition, Lp(a) level should be a marker of restenosis after percutaneous transluminal coronary angioplasty, saphenous vein bypass graft atherosclerosis, and accelerated coronary atherosclerosis of cardiac transplantation. However, limited data are available concerning the relation between Lp(a) and atherosclerosis of the thoracic aorta. Previous analyses have shown that the presence of atherosclerotic plaque in the thoracic aorta correlated with systemic embolism, and vascular disease and was a marker of CAD. Transesophageal echocardiography (TEE), which provides high-resolution imaging of the thoracic aorta, is a reliable tool to study the degree of thoracic aortic atherosclerosis. Using multiplane TEE, we hypothesized in this prospective study that Lp(a) is an independent marker of severity of thoracic aortic atherosclerosis.

*From the Department of Cardiology (Drs. Peltier, Iannetta Peltier, Lesbre, Colas and Tribouilloy), South Hospital, Amiens, France; and Division of Cardiovascular Diseases (Dr. Sarano), Mayo Clinic and Foundation, Rochester, MN.

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Correspondence to: Christophe Tribouilloy, MD, PhD, Service de Cardiologie, Hôpital Sud, 80054 Amiens, Cédex, France
Materials and Methods

Study Patients

Between September 1998 and January 2000, 119 consecutive patients > 40 years old considered for surgery or valvuloplasty for valvular heart disease underwent prospective multiplane TEE, coronary angiography, and measurement of plasma Lp(a) level. The diagnoses were mitral stenosis with or without mitral regurgitation in 12 patients, isolated pure mitral regurgitation in 29 patients, aortic stenosis with or without regurgitation in 49 patients, isolated aortic regurgitation in 14 patients, and combined mitral and aortic valve disease in 15 patients. Age, gender, lipid concentrations, and conventional cardiovascular risk factors for CAD were recorded. Blood was drawn after a 14-h overnight fast for determination of levels of serum total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and of triglycerides with standard methods. Diabetes mellitus was considered present if the fasting glucose level in the hospital was > 140 mg/dl or requiring previous or ongoing therapy. Systemic hypertension was defined as either systolic pressure > 140 mm Hg and/or diastolic pressure ≥ 90 mm Hg or elevation of diastolic or systolic pressure requiring pharmacologic therapy for BP control. A history of smoking was defined as ≥ 10 pack-years. Body mass index was computed as weight divided by height squared. A positive family history of CAD was defined as myocardial infarction or known CAD in a parent or sibling noted before the age of 65 years. Informed consent was obtained from each patient before the study.

Lp(a) Measurement

Conditions thought to influence Lp(a) concentrations, such as renal failure (serum creatinine level > 120 mol/L) or chronic inflammatory diseases, served as exclusion criteria. Blood was drawn after a 14-h overnight fast for assay of Lp(a). The Lp(a) content of serum samples was determined by an immunonephelometric technique (polyclonal antibodies [Behring Nephelometer II; Dade Behring; Deerfield, IL]). This assay detects Lp(a) at levels > 0.10 g/L and is strongly correlated with immunoradiometric or immunoenzymologic assays.

TEE Examination

Multiplane TEE was performed within 2 days of coronary angiography using ultrasonography (Sonos 2000 or 5500; Hewlett-Packard; Andover, MA) without procedural complications. A well-standardized protocol described previously was applied to cardiac examinations in all patients, especially for the study of thoracic aortic atherosclerosis. All studies were recorded on videotape and were interpreted independently by two experienced observers with excellent agreement in regard to the presence or absence of thoracic aortic atherosclerosis (100%). The presence, severity, and extent of thoracic aortic atherosclerosis were assessed with an aortic atherosclerotic score as previously described and coded as follows: first, < 0.10 g/L; second, 0.10 to 0.16 g/L; third, 0.17 to 0.23 g/L; fourth, 0.24 to 0.30 g/L; and fifth, > 0.30 g/L. All variables with a p < 0.10 in the univariate analysis were examined by multiple regression analysis. In this analysis, two models were used. In model 1, age, total cholesterol, LDL cholesterol, HDL cholesterol, diabetes, smoking, and systemic hypertension were included. In model 2, Lp(a) level was also added. Analysis was done with statistical software (Statview version 5; Abacus Concepts; Berkeley, CA).

Clinical Features

Of the 119 patients, 63 patients (53%) were men and 56 patients (47%) were women (mean age, 65.5 ± 12.3 years; range, 32 to 81 years). Hypertension was present in 45%, history of smoking was present in 35%, diabetes mellitus was present in 14%, and 24% had a family history of CAD. Mean body mass index was 25.9 ± 4.7 kg/m² (Table 1). Twenty-nine patients (24%) had Lp(a) levels ≥ 0.30 g/L. Mean levels of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides are reported in Table 1. Serum Lp(a) levels defined by quintile correlated significantly with age (p = 0.0037), total cholesterol (p = 0.03), and LDL cholesterol (p = 0.003). There was no relation between the Lp(a) levels and the presence or absence of diabetes, history of smoking, systemic hypertension, and family history of CAD.

Lp(a) and Thoracic Aortic Atherosclerosis

TEE examination detected thoracic aortic plaques in 75 patients (64%). The mean aortic atherosclerotic score was 4.8 ± 7.5 mm (range, 0.0 to 24.0 mm). Mean values of aortic atherosclerotic score for each quintile of patients on basis of Lp(a) are illustrated in Figure 1. By univariate analysis, age, systemic hyper-
tension, history of smoking, diabetes mellitus, and family history of CAD were significant markers of the presence of TAAP (Table 2). Higher Lp(a), total cholesterol, LDL cholesterol levels, and lower HDL cholesterol levels were also significant markers of TAAP (Table 2). There was a positive and significant linear correlation between the Lp(a) levels and the thoracic aortic score (p = 0.0001). In model 1 including conventional risk factors, age, total cholesterol, LDL cholesterol, HDL cholesterol, diabetes, smoking, and systemic hypertension were identified as independent predictors of aortic atherosclerotic score. In model 2 including conventional risk factors and Lp(a), Lp(a) was also identified as an independent predictor of aortic atherosclerotic score (Table 3).

**Lp(a) and CAD**

Coronary angiography revealed atherosclerotic coronary arteries in 56 of 119 patients (47%), mildly atherosclerotic coronary lesions in 19 patients (16%), one-vessel disease in 5 patients (4%), two-vessel disease in 21 patients (18%), and three-vessel disease in 11 patients (9%). The remaining 63 patients (53%) were found to have strictly normal coronary arteries angiographically evaluated. Patients with CAD had significantly more risk factors and higher Lp(a) levels (Table 2). There was a positive and significant correlation between the Lp(a) level and the coronary score (p = 0.0003). In model 1 including conventional risk factors, age, total cholesterol, LDL cholesterol, HDL cholesterol, diabetes, smoking, and systemic hypertension were identified as independent predictors of coronary score. In model 2 including conventional risk factors and Lp(a), Lp(a) was also identified as an independent predictor of coronary score (Table 3).

**Discussion**

Serum Lp(a) is a complex lipoprotein particle that consists of a LDL molecule in which the apolipoprotein B100 is linked to another large protein, the apolipoprotein(a), which has homology structure with plasminogen of the fibrinolytic system. Plasma levels vary widely among persons but are stable within individuals, suggesting a strong heritable component. Many studies have reported a strong relationship between coronary heart disease and certain apolipoprotein(a) isoforms of the protein than with others. Although numerous retrospective case control studies found an association between Lp(a) concentration and premature coronary heart disease, prospective studies provided controversial results. The conflicting results from the prospective studies may be the result of the use of different assay methods to determine Lp(a) levels and that different isoforms of the apolipoprotein(a) might have different atherogenic potential. Nevertheless, a meta-analysis of 27 prospective studies reported a clear association of Lp(a) with coronary heart disease, independent of the standard vascular risk factors. Our study confirms that Lp(a) level correlated well with the presence and severity of CAD angiographically evaluated. Many studies suggested that increased plasma Lp(a) levels were also related to the presence and the severity of extracranial carotid lesions, suggesting that Lp(a) is involved in the progression of carotid artery atherosclerosis. Rath et al showed a significant positive correlation between serum Lp(a) and apolipoprotein(a) in the arterial wall in biopsy samples obtained.
of the ascending aortas of patients undergoing aorticcoronary bypass surgery. High serum Lp(a) also led to significant increase of apolipoprotein B in the arterial wall. Both proteins were increased in aortic atherosclerotic plaques. The current prospective TEE study identified serum Lp(a) level in patients > 40 years old with valvular heart disease to be a marker of atherosclerotic aortic disease related to the severity of thoracic aortic atherosclerotic lesions, independent of age, gender, hypertension, history of smoking, lipid parameters, diabetes mellitus, and family history of CAD. This finding, consistent with the preliminary observation of Nishino et al., is likely applicable to other patient groups, but this remains to be proven.

In addition, our study confirms that conventional risk factors were also significantly related to the presence of aortic atherosclerosis. Although the exact mechanisms by which high plasma Lp(a) levels lead to increase atherosclerosis has not been fully elucidated, atherogenic effects of Lp(a) may result from the LDL-like properties and delivery of cholesterol at sites of vessel injury. As in the case of LDL, oxidation of Lp(a) seems to confer increased atherogenicity. Lp(a) has also thrombogenic properties because of the structural homology between apolipoprotein(a) and plasminogen. By competing with plasminogen in binding to fibrin, Lp(a) may hinder endogenous fibrinolysis. Although some studies did not report an association between serum cholesterol and Lp(a), a positive correlation with total cholesterol and LDL cholesterol was present in our study, as reported previously. As would be expected, no other interactions were noted with other cardiovascular risk factors. Unfortunately, the value of lowering Lp(a) in an attempt to decrease the cardiovascular events remains unknown. However, lowering of LDL cholesterol may decrease the pathogenicity of elevated Lp(a) levels. Patients with CAD or at risk of developing CAD and having high Lp(a) may benefit from lipid-lowering therapy, particularly in attempt to lower LDL cholesterol levels.

### Table 2—Univariate Analysis of Variables Related to the Patients with TAAP and With CAD*

<table>
<thead>
<tr>
<th>Variables</th>
<th>TAAP (n = 75)†</th>
<th>No TAAP (n = 44)</th>
<th>p Value</th>
<th>CAD (n = 56)‡</th>
<th>No CAD (n = 63)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>70.8 ± 8.5</td>
<td>56.5 ± 12.7</td>
<td>&lt;0.0001</td>
<td>70.2 ± 9.0</td>
<td>61.3 ± 13.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Male/female sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lp(a) &gt; 0.30 g/L</td>
<td>23 (31)</td>
<td>6 (14)</td>
<td>0.03</td>
<td>21 (37)</td>
<td>8 (13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>223 ± 41</td>
<td>202 ± 37</td>
<td>0.005</td>
<td>227 ± 40</td>
<td>205 ± 39</td>
<td>0.002</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>152 ± 37</td>
<td>120 ± 24</td>
<td>&lt;0.0001</td>
<td>151 ± 35</td>
<td>130 ± 34</td>
<td>0.0009</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>119 ± 58</td>
<td>104 ± 65</td>
<td>0.22</td>
<td>120 ± 60</td>
<td>108 ± 61</td>
<td>0.30</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15 (20)</td>
<td>2 (5)</td>
<td>0.02</td>
<td>13 (23)</td>
<td>4 (6)</td>
<td>0.008</td>
</tr>
<tr>
<td>Smoking</td>
<td>34 (45)</td>
<td>8 (18)</td>
<td>0.002</td>
<td>31 (55)</td>
<td>11 (17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>19 (25)</td>
<td>10 (24)</td>
<td>0.09</td>
<td>16 (28)</td>
<td>13 (14)</td>
<td>0.31</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>43 (57)</td>
<td>11 (25)</td>
<td>&lt;0.0001</td>
<td>33 (59)</td>
<td>21 (33)</td>
<td>0.005</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.6 ± 4.8</td>
<td>25.4 ± 3.6</td>
<td>0.37</td>
<td>26.0 ± 3.7</td>
<td>25.9 ± 5.2</td>
<td>0.92</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No. (%).
† Patients with an aortic atherosclerotic score > 0.
‡ Patients with a coronary score > 0.

### Table 3—Multiple Regression Analysis of Variables Related to Thoracic Aortic Atherosclerotic Score and Coronary Score*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Thoracic Aortic Atherosclerotic Score</th>
<th>Coronary Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>Age</td>
<td>0.561</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.387</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.425</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>−0.194</td>
<td>0.0355</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.267</td>
<td>0.0041</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.289</td>
<td>0.0039</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>0.306</td>
<td>0.0005</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>0.346</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Age, total cholesterol, LDL cholesterol, HDL cholesterol, diabetes, smoking, and systemic hypertension were included in model 1; in model 2, Lp(a) was also included. SC = standardized coefficient.
The present study has some limitations. It is possible, even with a multiplane probe, that we have slightly underestimated the incidence of atherosclerotic plaques in the aorta, especially in the upper ascending aorta due to the interposition of the trachea. The aortic atherosclerotic score selecting the largest plaques may also have underestimated or overestimated the severity of the thoracic aortic atherosclerosis, which is a diffuse but not an uniform process. However, no quantitative standard method has yet been established for assessing the severity of aortic atherosclerosis. Using the aortic score, we found a strong relation between the Lp(a) level and the severity of aortic atherosclerosis. Furthermore, atherosclerotic changes in the thoracic aorta have been widely studied using TEE, and an excellent reproducibility of transesophageal grading and stratification of atheroma in the thoracic aorta has been reported. In this study, patients were selected for valvular heart disease. Nevertheless, this group of valvular patients provided the opportunity to study a population almost similar to the general population for standard risk factors. The decision to forgo preoperative coronary angiography in patients with valvular disease is usually based on their clinical characteristics. However, patients > 40 years old considered for surgery or valvuloplasty were included in the current study in whom coronary angiography was systematically performed.

In conclusion, this study show that Lp(a) is an independent predictor of severity of thoracic aortic atherosclerosis in a population not selected for suspicion of CAD. This finding emphasizes the role of Lp(a) as a marker of atherosclerotic lesions in the major arterial locations.

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