Relation of Plasma Lipoprotein(a) to Infarct Artery Patency in Survivors of Myocardial Infarction

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Background. In the minutes to days after myocardial infarction, endogenous lysis of an occlusive coronary arterial thrombus occurs in most subjects. Compared with those in whom thrombolysis does not occur, those with antegrade flow in the infarct artery have improved left ventricular performance, less left ventricular dilatation, and improved survival. This study was performed to assess intrinsic hemostasis and fibrinolysis in survivors of myocardial infarction with or without antegrade perfusion of the infarct artery.

Methods and Results. In 105 survivors of infarction (75 men, 30 women; age, 30 to 80 years) not given thrombolytic therapy, coronary angiography revealed a patent (group 1, n=52) or occluded (group 2, n=53) infarct artery. Plasma concentrations of plasminogen, fibrinogen, tissue plasminogen activator activity, plasminogen activator inhibitor activity, cholesterol, triglycerides, and lipoproteins, including lipoprotein(a) (Lp[a]), were measured in blood procured 23±13 (mean±SD) months after infarction. Groups 1 and 2 were similar in age, sex, race, cardioactive medications, infarct artery, extent of coronary artery disease, and left ventricular performance. Of the plasma constituents assayed, the groups were similar except that Lp(a) averaged 18.5±21.7 mg/dL in group 1 and 49.1±44.8 mg/dL in group 2 (P<.001). This difference was evident in both Caucasian (n=65) (P=.009) and African American (n=40) (P=.01) subjects.

Conclusions. Survivors of myocardial infarction who failed to recanalize the infarct artery have higher plasma Lp(a) concentrations than those with a patent infarct artery. Lp(a) may inhibit intrinsic fibrinolysis. (Circulation. 1993;88:935-940.)

Key Words • fibrinolysis • thrombolysis • apolipoproteins

Thrombotic coronary arterial occlusion is the inciting pathophysiologic event in most subjects with Q-wave and non-Q-wave myocardial infarction. In many of these, endogenous fibrinolysis restores antegrade flow within minutes, hours, or days. In others, fibrinolysis does not occur, and the infarct artery remains occluded.1-4 If antegrade flow is restored within minutes, necrosis is confined to the subendocardium, and the extent of damage is limited.10,11 If antegrade flow is restored days after infarction, salvage of myocardium is minimal, but a salutary effect is observed nonetheless: left ventricular dilatation is diminished,12 the incidence of late potentials (by signal-averaged ECG) is reduced,13,14 and long-term survival is improved.15,17 Thus, spontaneous restoration of antegrade coronary flow, even if it occurs days after the acute event, exerts a beneficial influence on postinfarction morbidity and mortality.

Normally, homeostasis is maintained between thrombosis and thrombolysis, so that neither accelerated thrombosis nor excessive bleeding occurs. The formation and sustenance of an occlusive coronary thrombus may reflect enhanced thrombotic and/or inadequate fibrinolytic capacities. In support of this, survivors of myocardial infarction have reduced circulating plasminogen activator activity and elevated concentrations of plasminogen activator inhibitor.18 In addition, several studies have shown an association between high plasma concentrations of lipoprotein(a) (Lp[a]) and premature myocardial infarction.19-21 and recent in vitro data suggest that Lp(a) may promote thrombosis.22,23 The present study was performed to examine intrinsic hemostatic and fibrinolytic activities in survivors of myocardial infarction to determine whether plasma concentrations of substances known or suspected to be involved in hemostasis and fibrinolysis differ in subjects with patent and occluded infarct arteries.

Methods

Patient Population

The results of all cardiac catheterizations performed at Parkland Memorial Hospital and the Veterans Administration Medical Center, Dallas, Tex, from January
1988 to June 1991 were reviewed. Of the 2390 patients, 208 were identified who (1) were studied ≥7 days after first myocardial infarction, (2) did not receive thrombolytic therapy or have coronary angioplasty, (3) had a clearly discernible infarct artery (from review of the ECG, coronary angiogram, and left ventriculogram), and (4) were Caucasian (n=131) or African American (n=77). Only subjects who underwent coronary angiography ≥7 days after infarction were included, since previous studies showed that endogenous thrombolysis is completed in most individuals within 1 week of the event. Twenty-two subjects were excluded because of a chronic illness that might have influenced intrinsic hemostasis and fibrinolysis (ie, end-stage renal disease, malignancy, steroid-treated immunological disorder). On the basis of coronary angiography, the remaining 186 subjects were categorized as having (1) a patent infarct artery (group 1, n=92) or (2) an occluded infarct artery (group 2, n=94), and attempts were made to enlist their participation. Of the 186, 17 had died (4 from group 1, 13 from group 2); 18 could not be located (10 from group 1, 8 from group 2); and 46 chose not to participate (26 from group 1, 20 from group 2). The remaining 105 unrelated subjects (75 men, 30 women; age, 30 to 80 years) (52 in group 1, 53 in group 2) composed the study population. Of these, 65 were Caucasian, and 40 were African American. The time interval from infarction to the procurement of blood was 23±13 months (range, 5 to 44 months).

**Variables Assessed**

At catheterization, left ventricular ejection fraction was quantified by standard techniques from single-plane left ventriculograms. After coronary angiography, antegrade flow in the infarct artery was graded by the Thrombolysis in Myocardial Infarction (TIMI) criteria. Patients with grade 2 or 3 flow were said to have a patent infarct artery (group 1), and those with grade 0 or 1 flow were said to have an occluded artery (group 2). The presence of risk factors for atherosclerotic cardiovascular disease—systemic arterial hypertension, cigarette smoking, diabetes mellitus, family history, and elevated total cholesterol—was noted, and records were kept of each subject's cardiovascular medications.

Each participant answered a questionnaire regarding recent illnesses, current medications, and general condition. After an overnight fast, venous blood was obtained for determination of total cholesterol and triglycerides; very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol; plasminogen; fibrinogen; and Lp(a). Patients sampled between 8 and 10 AM (n=59) had additional blood collected for tissue plasminogen activator (t-PA) activity and plasminogen activator inhibitor (PAI) activity. The samples for t-PA activity were collected iniced acidified citrate tubes (American Diagnostica); the other samples were collected in tubes containing ethylenediamine tetraacetic acid (EDTA) or buffered citrate. Platelet-rich plasma was separated by centrifugation at 2000g for 20 minutes at 4°C. Platelet-poor plasma was prepared by centrifugation of the resulting supernatant at 12 000g for 15 minutes at 4°C. Aliquots of the resulting plasma fractions were taken, snap-frozen in liquid nitrogen, and maintained at −80°C until analysis.

Total cholesterol and triglycerides were measured by standard enzymatic methods (Boehringer Mannheim Biochemicals and Sigma Chemical Co). Lipoprotein cholesterol concentrations were measured according to the specifications of the Lipid Research Clinic in the laboratory of Dr Scott Grundy (University of Texas Southwestern Medical Center, Dallas, Tex).

Fibrinogen was measured by a standardized polymerization method (Dade Diagnostica, Aguada, Puerto Rico). The plasminogen assay was performed with samples incubated in an excess of streptokinase, and the plasmin-like activity was measured in the presence of a chromogenic substrate (Kabi Diagnostica, Helena Laboratories, Beaumont, Tex).

Plasminogen activator activity was determined with an indirect chromogenic assay by a modification of the method of Gething et al. Aliquots of acidified plasma were diluted 20× into assay buffer (0.1 mol/L Tris HCl, pH 7.5, with 0.1% Tween 80 [vol/vol]) containing a final concentration of 0.12 μmol/L lys-plasminogen (American Diagnostica), 0.4 mmol/L Spectrozyme-PL (American Diagnostica), and 25 μg/mL of the soluble fibrin monomer Desupil (American Diagnostica) in a final reaction volume of 100 μL in 96-well flat-bottom polystyrene microtitert plates. Absorbance at 405 nm (A_{405}) was monitored in a Thermomax (Molecular Devices) microtitert plate reader, and plasminogen activator activity was determined from the kinetic development of A_{405} calibrated against dilutions of a purified t-PA standard (supplied by Knoll Pharmaceuticals) using SOFTMAX (Molecular Devices) software.

PAI activity was quantified from the amount of urinary plasminogen activator (u-PA) neutralized in timed incubations. Dilutions (5 to 10×) of unacidified platelet-poor plasma samples in assay buffer were incubated with an equal volume of urokinase (10 U/mL) (Calbiochem) in a reaction volume of 50 μL in 96-well microtitert plates for 15 minutes at 37°C. Aliquots of the resulting mixture were then assayed for residual plasminogen activator activity in indirect chromogen assays, as described above. PAI activity is expressed in arbitrary units, with 1 AU defined as the amount neutralizing 1 U of u-PA activity. Duplicate assays were performed on each sample, and their values were averaged.

The plasma concentrations of Lp(a) were determined by a sandwich enzyme-linked immunosorbent assay (ELISA) (Gene Screen Laboratories, Dallas, Tex) according to the method of Menzel et al. and as previously described.

**Statistical Methodology**

All data are reported as mean±SD. All analyses were performed using BMDP (BMDP Statistical Software, Los Angeles, Calif). Groups 1 and 2 were compared with Student's t test for continuous variables and a χ² analysis for categorical variables. For variables with nonnormal distributions (eg, Lp[a]), a nonparametric analysis (Kruskal-Wallis or Mann-Whitney rank sum) was used. Further investigations, including the role of Lp(a) in infarct artery patency, were performed separately for Caucasians and African Americans because of known differences in Lp(a) distribution in these racial subgroups. The variables that were significantly different between those with patent and occluded in-
**Table 1. Comparison of Clinical and Angiographic Data for the Two Groups**

<table>
<thead>
<tr>
<th></th>
<th>Group 1* (n=52)</th>
<th>Group 2* (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>53±10</td>
<td>56±10</td>
</tr>
<tr>
<td>No. of men (%)</td>
<td>38 (73)</td>
<td>37 (70)</td>
</tr>
<tr>
<td>Estrogen-positive women (%)</td>
<td>5 (10)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Caucasians (%)</td>
<td>36 (69)</td>
<td>29 (55)</td>
</tr>
<tr>
<td>African Americans (%)</td>
<td>16 (31)</td>
<td>24 (45)</td>
</tr>
<tr>
<td>Q-wave infarction by ECG (%)</td>
<td>21 (40)</td>
<td>29 (55)</td>
</tr>
<tr>
<td>MI-to-catheterization interval (d)</td>
<td>22±2±5</td>
<td>27±3±3</td>
</tr>
<tr>
<td>Risk factors for ASCVD (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (52)</td>
<td>31 (58)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>32 (62)</td>
<td>32 (60)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (38)</td>
<td>11 (21)</td>
</tr>
<tr>
<td>Family history</td>
<td>29 (56)</td>
<td>31 (58)</td>
</tr>
<tr>
<td>Maintenance medications after MI (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>23 (44)</td>
<td>27 (51)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>25 (48)</td>
<td>25 (47)</td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>23 (44)</td>
<td>28 (53)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>44 (85)</td>
<td>41 (77)</td>
</tr>
<tr>
<td>Angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>61±14</td>
<td>55±13</td>
</tr>
<tr>
<td>Infarct artery (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>20 (38)</td>
<td>12 (23)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>17 (33)</td>
<td>20 (38)</td>
</tr>
<tr>
<td>Right</td>
<td>15 (29)</td>
<td>21 (40)</td>
</tr>
<tr>
<td>Extent of coronary artery disease (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-vessel</td>
<td>32 (61)</td>
<td>29 (55)</td>
</tr>
<tr>
<td>Two-vessel</td>
<td>15 (29)</td>
<td>17 (32)</td>
</tr>
<tr>
<td>Three-vessel</td>
<td>5 (10)</td>
<td>7 (13)</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; ASCVD, atherosclerotic cardiovascular disease. All data are mean±SD. P=NS for all parameters.

*Group 1 patients had patent infarct-related arteries; group 2 patients had occluded infarct-related arteries.

Left ventricular ejection fraction in multiple univariate analyses were submitted to multivariate analysis using a stepwise logistic regression. For all analyses, a value of P<.05 was considered significant.

**Results**

The clinical and angiographic data for groups 1 and 2 are displayed in Table 1. The groups were similar in age, sex, race, risk factors for atherosclerotic cardiovascular disease, cardiovascular medications, left ventricular ejection fraction, and extent and location of coronary artery disease.

A total of 18 subjects (9 from each group) received maintenance hypolipidemic medications: 11 received lovastatin (6 from group 1, 5 from group 2), 4 received cholestyramine (2 from group 1, 2 from group 2), and 3 received gemfibrozil (1 from group 1, 2 from group 2). None received nicotinic acid.

Groups 1 and 2 had similar plasma concentrations of total cholesterol and triglycerides; VLDL, LDL, and HDL cholesterol; plasminogen; fibrinogen; t-PA activity; and PAI activity (Table 2). However, the groups were distinctly different with regard to plasma concentrations of Lp(a) (Table 2). The mean plasma Lp(a) concentrations in the subjects with persistent coronary arterial occlusion were more than twice those of subjects who regained infarct artery patency. This difference in plasma concentrations of Lp(a) was present when Caucasian and African American subgroups were analyzed separately (Table 3).

The vast majority of group 1 patients (88%) did not have collateral filling of the distal infarct artery, whereas most group 2 subjects (83%) had visible collaterals. It is not surprising, therefore, that those with collateral filling had higher plasma Lp(a) concentrations than those in whom collaterals were absent (43.6±40.5 vs 25.2±34.4 mg/dL, P=.004).

By stepwise logistic regression analysis, the plasma concentration of Lp(a) was the only significant predictor of infarct artery patency in Caucasians. In African Americans, infarct artery patency was related significantly to the plasma concentration of Lp(a); age was a weak (but significant) predictor of infarct artery patency. No other variable was significant by univariate or multivariate analysis.

**Table 2. Comparison of Blood Values for the Two Groups**

<table>
<thead>
<tr>
<th>Assay</th>
<th>Group 1* (n=52)</th>
<th>Group 2* (n=53)</th>
<th>Ratio (occluded/patent)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>209±46</td>
<td>211±43</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>182±118</td>
<td>196±114</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Very-low-density lipoprotein</td>
<td>32±24</td>
<td>33±21</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>140±38</td>
<td>141±39</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>38±10</td>
<td>38±12</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td>18.5±21.7</td>
<td>49.1±44.8</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Plasminogen</td>
<td>120±18</td>
<td>111±17</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>321±60</td>
<td>330±66</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Tissue plasminogen activator</td>
<td>0.22±0.06†</td>
<td>0.24±0.08‡</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Plasminogen activator inhibitor</td>
<td>7.37±3.40†</td>
<td>8.03±3.99‡</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Results are expressed in mg/dL except for tissue plasminogen activator (IU/mL) and plasminogen activator inhibitor (AIU/mL). All data are mean±SD.

*Group 1 patients had patent infarct-related arteries; group 2 patients had occluded infarct-related arteries.

**Table 3. Plasma Concentrations of Lipoprotein(a) According to Race**

<table>
<thead>
<tr>
<th></th>
<th>Group 1* (n)</th>
<th>Group 2* (n)</th>
<th>Ratio (occluded/patent)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>15.1±22.4 (36)</td>
<td>37.1±38.4 (29)</td>
<td>2.5</td>
<td>.009</td>
</tr>
<tr>
<td>African American</td>
<td>26.2±18.5 (16)</td>
<td>63.7±48.4 (24)</td>
<td>2.4</td>
<td>.01</td>
</tr>
<tr>
<td>Total</td>
<td>18.5±21.7 (52)</td>
<td>49.1±44.8 (53)</td>
<td>2.6</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Results are expressed in mg/dL. All data are mean±SD.

*Group 1 patients had patent infarct-related arteries; group 2 patients had occluded infarct-related arteries.
Discussion

In most subjects with myocardial infarction, the inciting pathophysiological event is an occlusive coronary arterial thrombus. In some of these individuals, endogenous thrombolysis occurs within minutes to hours; necrosis is confined to the subendocardium, and a non-Q-wave infarction occurs. In others, the occlusive thrombus persists for hours to days, resulting in a Q-wave infarction. Even in about 50% of these patients, spontaneous thrombolysis restores antegrade flow within 1 week of the event. Thus, in most survivors of myocardial infarction, coronary arterial thrombosis is the initiating event, but endogenous thrombolysis restores antegrade flow within hours to days. Antegrade perfusion of the infarct artery favorably influences long-term morbidity and mortality; compared with those whose infarct artery is occluded, those with antegrade flow have less left ventricular dilatation, improved regional left ventricular performance, a lower incidence of late potentials by signal-averaged ECG, and improved survival.

Previous studies have suggested that an imbalance of intrinsic fibrinolytic and prothrombotic activity may be contributory in patients with unstable angina, myocardial infarction, saphenous vein graft occlusion after bypass surgery, and fatal cardiovascular events. However, no study has examined fibrinolytic or prothrombotic activity in survivors of infarction in whom the angiographic status of the infarct artery was known. Our data demonstrate that those with a patent infarct artery (group 1, n=52) and those with an occluded artery (group 2, n=53) have similar plasma concentrations of total cholesterol and triglycerides; VLDL, LDL, and HDL cholesterol; plasminogen; fibrinogen; t-PA activity; and PAI activity (Table 2). In contrast, they are distinctly different with regard to plasma concentrations of Lp(a); those with a patent artery have lower Lp(a) concentrations than those with an occluded artery (Table 3). Importantly, this difference was seen in both the Caucasian and African American subgroups (Table 3).

The plasma concentration of Lp(a) varies over a wide range among individuals but is remarkably constant throughout a healthy individual’s lifetime. Plasma concentrations of Lp(a) are relatively uninfluenced by age or sex, with the exception of postmenopausal women, whose plasma Lp(a) levels are somewhat higher than those of premenopausal women. The distribution of plasma Lp(a) concentrations varies greatly among different ethnic groups: African Americans have a nearly symmetrical distribution, whereas Caucasians, Orientals, and Asian Indians have distributions that are highly skewed toward lower levels. In healthy volunteers, plasma Lp(a) concentrations, on average, are about twice as high in African Americans as in Caucasians. For these reasons, it was essential to analyze the Lp(a) data of Caucasians and African Americans separately.

Lp(a) is a plasma lipoprotein composed of an LDL particle and a unique glycoprotein, apolipoprotein(a) (apo(a)). Apo(a) shares remarkable structural similarities to the plasma zymogen, plasminogen. Apo(a) has multiple repeated domains (so-called kringle) that are homologous to the fibrin-binding domains of plasminogen. Plasminogen plays a key role in the fibrinolytic system, and it has been postulated that high concentrations of Lp(a) may hinder fibrinolysis by molecular mimicry. Since apo(a) is very similar to plasminogen, high concentrations of Lp(a) may competitively or uncompetitively inhibit the actions of plasminogen. In vitro studies, Lp(a) has been shown to interfere with several steps in the fibrinolytic pathway. First, high concentrations of Lp(a) inhibit the binding of plasminogen to endothelial cells, mononuclear cells, and platelets; this may interfere with plasminogen activation on the endothelial surface and the lysis of platelet-rich thrombi. Second, Lp(a) competitively inhibits the binding of plasminogen and t-PA to fibrin, thereby interfering with plasminogen activation on the surface of the thrombus. Third, Lp(a) binds to cell-surface glycosaminoglycans, including heparin and heparin sulfate, which normally inhibit thrombin formation.

Fourth, Lp(a) may interfere with the binding of plasminogen to its activator. Lp(a) competitively inhibits the binding of plasminogen to streptokinase by forming an Lp(a)/streptokinase complex. t-PA binds reversibly to surface-bound Lp(a), thereby inhibiting plasminogen activation; a similar interaction may occur in vivo. Thus, the structural similarity of Lp(a) and plasminogen may allow the former to compete with the latter for cellular receptors, fibrin, and t-PA, thereby diminishing plasminogen activation, plasmin production, and, ultimately, fibrinolysis.

Our study has limitations. First, of the 186 subjects who fulfilled the entrance criteria, blood was obtained from 105. Of the 81 subjects not studied, 40 had a patent infarct artery, and 41 had an occluded infarct artery. Although unlikely, it is possible that selection bias was introduced by our inability to procure blood in the remaining subjects. Second, 18 subjects (9 in each group) received lipid-lowering agents, which may have influenced the plasma concentrations of total cholesterol, triglycerides, and HDL, LDL, and VLDL cholesterol. However, none received medications known to influence the plasma concentrations of Lp(a) (eg, nicotinic acid). Third, the time interval from infarction to blood sampling varied from 5 to 44 months. Although it is conceivable that the nonuniformity of this time interval may have influenced our results, previous studies have shown that the plasma Lp(a) concentration is remarkably constant throughout a person’s lifetime. Plasma levels of Lp(a) acutely rise and remain elevated for weeks after infarction; however, since blood was procured ≥5 months after a coronary event, the “acute-phase” elevation of Lp(a) associated with myocardial infarction was avoided. Lastly, we measured plasma Lp(a) concentrations in survivors of a first myocardial infarction in whom we assessed the patency (or lack thereof) of the infarct artery. All patients had coronary angiography 7 to 118 days after infarction. Although it is possible that some of our 105 subjects may have had recurrent ischemic events in the period between coronary angiography and blood sampling, such events would not have influenced the plasma Lp(a) concentration or the status of the infarct artery within the 4 months of first infarction.

In conclusion, our study provides the first in vivo evidence that elevated concentrations of Lp(a) may inhibit fibrinolysis. As a result, the survivor of myocardial infarction with an elevated plasma concentration of...
Lp(a) is more likely to have a persistently occluded infarct artery, leading, in turn, to an increased risk of left ventricular dilatation and sudden death. In contrast, in the survivor of infarction with a relatively low plasma concentration of Lp(a), endogenous thrombolysis is more likely, resulting in antegrade perfusion of the infarct artery and improved survival. Further studies are needed to elucidate the clinical utility of measuring plasma Lp(a) not only as a risk factor for coronary atherosclerosis but also as a prognostic factor in survivors of myocardial infarction.

Acknowledgments
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