Predictors of Adverse Long-Term Outcome in Acute Myocardial Infarction Patients Undergoing Primary Percutaneous Transluminal Coronary Angioplasty
— With Special Reference to the Admission Concentration of Lipoprotein (a) —

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The predictive values for long-term outcome in 127 consecutive patients with acute myocardial infarction (AMI) after successful primary percutaneous transluminal coronary angioplasty (PTCA) were prospectively investigated in the present study. The primary endpoint was a composite of cardiac death, nonfatal AMI, and recurrent angina. Follow-up angiography was performed in 120 patients to assess restenosis. The primary endpoint occurred in 21 patients during a follow-up period of 35±24 months. These patients had a higher lipoprotein(a) [Lp(a)] concentration (p=0.0105) and more prevalence of multivessel disease (p=0.0028) than the other patients. The subjects were divided into 2 groups at the 75th percentile Lp(a) value: group A had an Lp(a) concentration ≥47 mg/dl and group B <47 mg/dl. Kaplan-Meier analysis showed a lower cardiac event-free survival rate in group A (p=0.0007) and in patients with multivessel disease (p=0.001). In Cox proportional hazards regression analysis, an Lp(a) level ≥47 mg/dl (relative risk [RR] 5.5, 95% confidence interval [CI] 2.0–15.0, p=0.0007) and multivessel disease (RR 5.3, 95% CI 2.0–13.7, p=0.0006) were independent predictors of the primary endpoint. An elevated Lp(a) concentration on admission and multivessel disease are significant predictors for long-term adverse outcome in AMI patients treated by primary PTCA. (Circ J 2003; 67: 605–611)

Key Words: Acute myocardial infarction; Lipoprotein(a); Percutaneous transluminal coronary angioplasty; Prognosis

An elevated concentration of lipoprotein(a) [Lp(a)] is associated with an increased prevalence and severity of coronary artery disease (CAD)1–5. Percutaneous transluminal coronary angioplasty (PTCA) is an established treatment for CAD and several investigators have reported that an elevated Lp(a) concentration is a risk factor for the progression of CAD or its clinical recurrence after PTCA.6–8 Restenosis of the treated coronary lesion after PTCA remains the major long-term complication of this procedure, but the relationship between Lp(a) and restenosis is still controversial9–12.

In patients with acute myocardial infarction (AMI), primary PTCA has been shown recently to reduce the hospital mortality rate, and the initial benefits of primary PTCA are maintained over a period of several years13–18. The influence of Lp(a) on the long-term prognosis of AMI, which may be associated with the progression of CAD or with restenosis, remains unclear. In the present study, we investigated the long-term prognostic importance of the serum Lp(a) concentration after successful primary PTCA for AMI in terms of its influence on cardiac death, nonfatal AMI, recurrent angina, and restenosis.

Methods

The study subjects consisted of consecutive patients with AMI who underwent primary PTCA between January 1996 and June 2001. Informed consent was obtained from all of the patients. Criteria for inclusion in the study were: (1) ST segment elevation of at least 1 mm in 2 or more adjacent leads on the admission electrocardiogram (ECG), (2) Thrombolysis in Myocardial Infarction (TIMI) flow grade ≥II with less than 50% stenosis of the infarct-related artery by primary PTCA, and (3) recanalization of the infarct-related artery by primary PTCA within 12 h of onset. Criteria for exclusion were: (1) concomitant severe disease such as malignancy and (2) death during the index hospital stay within 30 days of admission. During the study period, 142 patients were referred for primary PTCA based on these criteria. PTCA was unsuccessful in 6 patients (4.2%) and 3 patients (2%) died within 30 days of PTCA; 3 patients (2%) had malignancy and a life expectancy of less than 6
months and 3 other patients (2%) were lost to follow-up. The remaining 127 patients were enrolled in this study.

Coronary Angiography

Coronary angiography and primary PTCA were performed in a routine manner. Coronary angiograms of the contralateral coronary artery were initially obtained to evaluate collateral flow\(^{19}\) and then the TIMI flow grade of the infarct-related coronary artery was determined\(^{20}\). The first balloon inflation was performed an average of 87± 61 min after presentation at the emergency room. Successful PTCA was defined as residual stenosis of less than 50% with a TIMI flow grade \(\geq II\). When this angiographic goal could not be achieved by angioplasty alone, or when PTCA was complicated by dissection or reocclusion, a stent was used; 54 patients (43%) received at least 1 stent. All patients were treated with aspirin (162 mg/day), and stented patients were also treated with ticlopidine (200 mg/day) for 4 weeks, if there were no contraindications to these drugs.

Predischarge coronary angiography and contrast left ventriculography were performed in all patients. When necessary, patients with multivessel disease underwent additional PTCA of the noninfarct-related coronary artery (this was done in 9 patients). The left ventricular ejection fraction was determined by contrast left ventriculography. Angiographic follow-up was performed in 120 (94%) patients at the 6th month post discharge or earlier if symptoms recurred.

Coronary angiograms were carefully reviewed by 3 experienced investigators who were unaware of any other data of the patients. The TIMI flow grade was determined by consensus. Two of the investigators used calipers to measure the severity of stenosis, as described previously\(^{21}\). Restenosis was defined as \(\geq 50\%\) stenosis in infarct-related lesion at follow-up examination and significant coronary stenosis was defined as \(\geq 75\%\) stenosis.

Determination of Lipid Concentrations

Lipid concentrations were measured with a Hitachi 7250 autoanalyzer, which measured total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) concentrations by an enzymatic method. Lp(a) was measured by a latex-enhanced turbidimetric immunoassay, as reported previously\(^{22}\). Serum for the measurement of these lipids was harvested immediately after admission. The concentrations of TC, TG and HDL-C were also measured just before discharge.

Data Collection and Long-Term Follow-up

Data were collected prospectively. For 6 months, all patients were reviewed monthly at the outpatient clinic and thereafter, they were followed at the clinic or by their medical practitioner. Data were obtained from hospital charts and were supplemented by local physicians as well as by telephone interview with the patient or relatives. Follow-up data included information about cardiac death, nonfatal AMI, recurrent angina, and restenosis.

The primary endpoint was cardiac death, nonfatal AMI, or recurrent angina. Cardiac death was defined as death from pump failure, sudden cardiac death or death because of arrhythmia. Recurrent AMI was defined as recurrent chest pain lasting more than 30 min with ST–T changes and either emergency angiographic confirmation of an occluded vessel or elevation of creatine kinase to more than twice the upper limit of normal. Chest pain accompanied by ST–T change on the ECG was classified as recurrent
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angina if infarction was ruled out.

Other Variables

Demographic data, traditional risk factors, and clinical variables were evaluated to control for confounding factors. These were age, sex, diabetes mellitus (fasting glucose ≥126 mg/dl or glucose concentration following a 75-g glucose load ≥200 mg/dl), hypertension (history of a systolic blood pressure ≥160 mmHg or a diastolic blood pressure ≥90 mmHg), hypercholesterolemia (≥240 mg/dl or use of cholesterol-lowering medications), number of diseased vessels, Killip class, reperfusion time (the time from the onset of symptoms to achievement of TIMI grade II or III flow), the door to balloon time (time from admission to the first balloon inflation), and left ventricular ejection fraction (LVEF) evaluated by contrast left ventriculography.

Statistical Analysis

Data are expressed percentages for discrete variables, and as the mean±SD or median with the 25th and 75th percentiles for continuous variables. Categorical variables were measured between 2 groups by the chi-square test or Fisher’s exact test, as appropriate. Continuous variables with a normal distribution were compared using Student’s two-tailed t-test. If the distribution was not normal, a nonparametric method was used (Mann-Whitney U test). Cardiac event-free survival was examined by the Kaplan-Meier method and the log-rank test. Multivariate analysis of the predictors of long-term cardiac event-free survival was performed using a Cox proportional hazards regression model. We performed stepwise regression of all variables with a p value <0.10 in the univariate analysis as well as variables of known clinical importance (age ≥70 years, gender, multivessel disease, anterior infarction, hypertension, diabetes mellitus, current smoking, hypercholesterolemia, Killip class ≥III, LVEF <40%, collateral grade, stent use, and Lp(a) ≥47 mg/dl). Because an Lp(a) concentration of 46.7 mg/dl was the 75th percentile of the study population, we defined subjects with Lp(a) ≥47 mg/dl as the high Lp(a) group. Relative risk and 95% confidence intervals (CI) were determined. Data were analyzed using the Stat View 5.0 statistical software (1998; SAS Institute Inc, Cary, NC, USA). A p value of <0.05 was accepted as indicating significance.

Results

Clinical Characteristics

The mean age of the study population was 66±11 years. The median serum Lp(a) concentration was 23 mg/dl (interquartile range: 15–47). Table 1 summarizes the baseline characteristics of subjects stratified by Lp(a) concentration and clinical variables.

Table 2 Baseline Clinical Characteristics of the Patients Stratified by the Lp(a) Concentration

<table>
<thead>
<tr>
<th>Lp(a) Concentration</th>
<th>Group A (n=31)</th>
<th>Group B (n=96)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64±8</td>
<td>67±7</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>23 (74%)</td>
<td>81 (84%)</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>201±32</td>
<td>181±56</td>
<td>0.0059</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>46±9</td>
<td>46±12</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>88 (70,120)</td>
<td>85 (68,123)</td>
<td>NS</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>23 (74%)</td>
<td>63 (66%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (65%)</td>
<td>55 (57%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (26%)</td>
<td>28 (29%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>18 (58%)</td>
<td>22 (23%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Killip class ≥III</td>
<td>3 (10%)</td>
<td>9 (9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>11 (36%)</td>
<td>18 (19%)</td>
<td>0.0028</td>
</tr>
<tr>
<td>Initial TIMI flow ≥II</td>
<td>3 (10%)</td>
<td>13 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>Reperfusion time (min)</td>
<td>249±126</td>
<td>271±148</td>
<td>NS</td>
</tr>
<tr>
<td>Door to balloon time (min)</td>
<td>89±63</td>
<td>87±61</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>49±12</td>
<td>50±11</td>
<td>NS</td>
</tr>
<tr>
<td>Stenting</td>
<td>15 (48%)</td>
<td>39 (41%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

ACEI, Angiotensin-converting enzyme inhibitor; HDL-C, high-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; TIMI, Thrombolysis in Myocardial Infarction. Data for triglyceride and lipoprotein(a) are the median and interquartile range.
Serum Lp(a) Concentration and Long-Term Outcome

An elevated Lp(a) concentration was defined as ≥47 mg/dl, which was the 75th percentile value of Lp(a) in the study population. The clinical parameters of group A [Lp(a) ≥47 mg/dl] and group B [Lp(a) <47 mg/dl] are shown in Table 2. Group A had a higher prevalence of hypercholesterolemia (58% vs 23%, p=0.0002) and statin use (45% vs 15%, p=0.0004). The admission concentration of TC of group A was significantly higher than that of group B (201±32 mg/dl vs 181±36 mg/dl, p=0.0069). However, the concentration of TC just before discharge did not differ between the 2 groups.

A primary endpoint was detected in 21 patients during a mean follow-up period of 35±24 months (Table 3). Five patients died of cardiac death (1 sudden death, 1 death from heart failure, and 3 fatal AMI) and 6 died from non-cardiac causes (gastric cancer 1, pneumonia 1, stroke 1, lung cancer 1, interstitial pneumonia 1, and sepsis 1). Recurrent MI occurred in 4 patients (12.9%) from group A and 4 patients (4.2%) from group B. Overall, there were 5 (3.9%) cardiac deaths and 6 (4.8%) non-cardiac deaths during the follow-up period, so the mortality rate was 8.7%. The incidence of recurrent angina was significantly higher in group A than group B (25.8% vs 3.1%, p=0.0006). The 19 patients with recurrent angina and MI all underwent coronary angiography and angiographic progression was found in all of them: an infarct-related lesion in 7 (37%) and a noninfarct-related coronary artery in 12 (63%). The 21 patients (16.5%) with a primary endpoint comprised 12 (38.7%) from group A and 9 (9.4%) from group B (p=0.0003).

Follow-up angiography was performed in 120 patients and restenosis was found in 38 patients (31.7%): 8 (26.7%) from group A and 30 (33.3%) from group B (p=NS).

Long-Term Cardiac Event-Free Survival

Kaplan-Meier survival analysis revealed that group A (p=0.0007, Fig 1) and patients with multivessel disease (p=0.001, Fig 2) had a significantly lower event-free survival rate. In 98 patients without multivessel disease, Kaplan-Meier survival analysis also revealed that patients with Lp(a) ≥47 mg/dl had a significant lower event-free survival rate (Fig 3). Cox multiple regression analysis identified an Lp(a) concentration ≥47 mg/dl (relative risk 5.5, 95%CI 2.1–15.0, p=0.0007) as an independent predictor of the primary endpoint, followed by multivessel disease (relative risk 5.3, 95%CI 2.0–13.7, p=0.0006).
Discussion

Long-Term Outcome After Primary PTCA

Primary PTCA without antecedent thrombolytic therapy is an effective mean of achieving coronary reperfusion in patients with AMI and several studies have demonstrated a beneficial effect of primary PTCA on the long-term outcome as well as the in-hospital outcome of AMI. In a recent report from the New York coronary angioplasty registry based on 2,291 patients who underwent primary PTCA, the 3-year mortality rate for these patients was 12.6%, and the long-term risk factors with the highest risk ratio (RR) were shock (RR 4.61), dialysis (RR 3.45), and left main trunk disease (RR 2.88). In The Angioplasty in Myocardial Infarction Trial, the 2-year mortality rate of patients randomized to PTCA was 6.2%, and predictors of death or reinfarction at 2 years were hypertension, smoking, time to randomization, and the TIMI flow grade after angioplasty. It has been reported that conventional risk factors, such as hypertension, diabetes mellitus, TC, HDL- and low density lipoprotein-cholesterol (LDL-C), and smoking habit, were not significant predictors for the second MI. The angiographic no-reflow phenomenon after PTCA is reported to be a predictor of the long-term cardiac outcome in patients with AMI, with the 5.8-year overall and cardiac mortality rates being 23% and 16%, respectively. In the present study, there was no association between cardiac events and the TIMI flow grade after PTCA, and the rate of achieving TIMI grade II flow in the high Lp(a) group did not differ from the rate in their counterparts.

Although an elevated Lp(a) concentration is a significant risk factor for the first MI, few data exist on the relationship between Lp(a) and the long-term prognosis of AMI after successful primary PTCA. The present study demonstrated that the 35-month overall and cardiac mortality rates were 8.7% and 3.9%, respectively, and that a high Lp(a) concentration was significantly associated with an adverse long-term cardiac outcome.

Lp(a) as a Risk Factor for CAD

Previous long-term observational studies have reported that Lp(a) is a significant predictor of the risk of future CAD in men and women. Plasma Lp(a) concentrations have also correlated with the number, severity, and length of coronary lesions. Furthermore, high Lp(a) concentrations have been detected in patients with their first AMI. Among patients scheduled for elective PTCA, rapid angiographic progression was found in 27% and the Lp(a) concentration was clearly elevated in such patients. In addition, the Lp(a) concentration has been reported to be a significant risk factor for clinical recurrence within 6 months of PTCA. However, the relationship between Lp(a) and restenosis after PTCA is still controversial. In the present study, a high Lp(a) concentration was an independent predictor of a composite endpoint for cardiac events. Subgroup analysis showed that recurrent angina was more prevalent in the high Lp(a) group than in the low Lp(a) group. Among the 120 patients undergoing follow-up angiography, the restenosis rate was similar between the high Lp(a) and low Lp(a) groups. Repeat coronary angiography was performed in all 19 patients with recurrent AMI or recurrent angina, and progression of CAD in the non-PTCA coronary artery was found in 12 (63%) of them. These results suggest that a high Lp(a) concentration may be associated with the progression of coronary atheroma, but not with restenosis. Measurement of Lp(a) seems to allow a more accurate assessment of an individual’s risk of recurrent angina or progression of coronary disease.

Interaction of Lp(a) With Other Risk Factors

Among 31 patients with Lp(a) concentrations at or above the 75th percentile, the TC concentration and the frequency of subsequent statin therapy were higher than in the group with Lp(a) less than the 75th percentile. Several other studies have shown that patients with high Lp(a) concentrations have significantly higher concentrations of TC or LDL-C than their counterparts. In addition, the HERS study showed that patients from the highest Lp(a) quintile were likely to be receiving lipid-lowering agents. It is still unclear how Lp(a) and LDL-C interact to produce a pathological effect. The mechanisms underlying concomitant elevation of Lp(a) and TC or LDL-C are also unknown. On the other hand, there is a significant interaction between traditional risk factors and Lp(a) when predicting the occurrence of coronary events. Elevated Lp(a) concentrations may provoke the coronary risk related to high concentration of LDL-C, hypertension, or a combination of risk factors. Therefore, because Lp(a) can markedly increase the risk of coronary events in the presence of additional coronary risk factors, it is imperative to strictly control such risk factors in individuals with an elevated Lp(a) concentration.

Possible Pathophysiological Mechanism

Although the unique structural features of Lp(a) suggest both a thrombogenic and an atherogenic potential, its precise mechanism of action is still uncertain. The deposition of Lp(a) has been documented in human aortic and coronary atherosclerotic plaques. Enhanced macrophage infiltration into atherosclerotic plaques has been associated with the development of acute coronary syndrome. Macrophages have also been implicated in the onset of plaque rupture through digestion of the fibrous cap. Dangas et al investigated the presence and extent of Lp(a) by morphometric analysis of immunostained human coronary atherectomy specimens and found that Lp(a) was ubiquitous in human coronary atheroma and detectable in larger amounts in the tissues from the culprit lesions of patients with unstable angina than in those with stable angina. Furthermore, the detection of plaque Lp(a) correlated with the amount and location of macrophage infiltration. Such colocalization of Lp(a) and macrophages provides support for earlier in vivo data suggesting that the apoprotein(a) portion of unoxidized Lp(a) acts as a chemotactic.
Study Limitations

Our study population was relatively small, which may have limited the statistical power for detecting the predictors of long-term survival. However, long-term follow-up data were available for 98% of the subjects, and nearly 90% continued to attend hospital after disease onset. Thus, we obtained most of the data by reviewing the hospital charts or by direct interview with the patients. Accordingly, we believe that the quality of the data is sufficiently high and that any bias produced by interhospital differences is minimal.

Although the serum Lp(a) concentration is known to be under genetic control and is relatively constant throughout life, the serum Lp(a) gradually increases for several days after AMI and then returns to the initial concentration after 1 month. In patients with unstable or AMI, the Lp(a) concentration measured immediately after admission is similar to that in the chronic stable phase. Therefore, to minimize the effect of acute-phase reaction to AMI, blood for measurement of Lp(a) and other lipids was collected immediately after each patient entered the emergency room.

The high Lp(a) group (≥47 mg/dL) had a higher prevalence of hypercholesterolemia and statin therapy than the low Lp(a) group (<47 mg/dL). The TC concentration just before discharge did not differ between the 2 groups and statin therapy may explain this lack of a difference. Statins were given on the basis of the concentration of TC and not Lp(a).

Conclusion

The present study demonstrated that the admission Lp(a) concentration and multivessel disease are significantly associated with an adverse long-term cardiac event. Because Lp(a) may further increase the risk of coronary events in patients who have a high global cardiovascular risk, it is important to strictly control additional risk factors in these patients after successful primary PTCA.

References


