Serum lipoprotein(a) concentrations are related to coronary disease progression without new myocardial infarction

Akira Tamura, Toru Watanabe, Yoshiaki Mikuriya, Masaru Nasu

Abstract

Objective—To examine the association between serum lipoprotein(a) and angiographically assessed coronary artery disease progression without new myocardial infarction.

Patients and design—85 patients with coronary artery disease who underwent serial angiography with an interval of at least two years were studied. Progression of coronary artery disease was defined as an increase in diameter stenosis of 15% or more. Vessels on which angioplasty had been performed were excluded from the analysis. The patients were classified into two groups: a progression group without new myocardial infarction (n = 48) and non-progression group (n = 37). Risk factors including lipoprotein(a) were evaluated to see how they were related to progression without myocardial infarction.

Results—There were no differences between the two groups in the following factors: age, gender, the time interval between the angiographic studies, the distribution of the analysed coronary arteries, and history of well established coronary risk factors. Univariate analysis showed that serum lipoprotein(a) ($P = 0.0002$), cigarette smoking between the studies ($P = 0.002$), serum high density lipoprotein ($P = 0.003$), and serum low density lipoprotein ($P = 0.01$) were related to progression without myocardial infarction. Multivariate analysis selected two independent factors for progression without myocardial infarction: serum lipoprotein(a) ($P = 0.003$) and serum high density lipoprotein ($P = 0.03$).

Conclusions—Serum lipoprotein(a) concentrations are closely related to the progression of coronary artery disease without new myocardial infarction. Lipoprotein(a) lowering treatment may be needed to prevent disease progression in patients with coronary artery disease and high serum lipoprotein(a).

(Br Heart J 1995;74:365-369)

Keywords: risk factors, coronary artery disease, lipoprotein(a), angiography

Lipoprotein(a) is a low density lipoprotein-like particle with one additional molecule of apoprotein(a) linked to apoprotein B by a

disulphide bond. Previous studies¹⁻⁷ have shown a positive correlation between serum lipoprotein(a) concentration and the risk of coronary artery disease. However, it is unclear whether raised serum lipoprotein(a) is related to future myocardial infarction or progression of coronary artery disease. This study was conducted to clarify the relationship between serum lipoprotein(a) and angiographically assessed coronary artery disease progression. The mechanism of coronary disease progression without new myocardial infarction appears to differ from that of progression with new myocardial infarction and that of progression from any degree of stenosis to total occlusion without clinical evidence of new myocardial infarction: the latter is more related to thrombosis than the former. Therefore, we studied only patients with disease progression in the absence of new myocardial infarction or new total occlusion.

Methods

PATIENTS

From April 1992 to March 1994, patients with coronary artery disease who were followed at Oita Medical University and who met the following criteria were selected into this study: (1) a period of at least two years since the time of the previous coronary angiographic study, regardless of the presence or absence of ischaemic signs; (2) no previous coronary bypass surgery; (3) no evidence of familial hypercholesterolaemia; and (4) no evidence of chronic liver disease or chronic renal failure. There were 95 patients who met the above criteria. Seven patients without ischaemic symptoms refused repeated coronary angiography. Eighty eight patients underwent repeated coronary angiographic studies. Two patients with new myocardial infarction and one patient with progression to total occlusion without clinical evidence of new myocardial infarction were excluded from this study. Thus a total of 85 patients (72 men and 13 women with a mean age of 63 years) was included in this study. Twenty six patients underwent repeated angiography because of recurrent anginal attacks, while 59 had no ischaemic symptoms. No patient had increased C reactive protein at the time the blood was sampled for serum lipoprotein(a) measurement. Written informed consent was obtained from all patients.

CORONARY ANGIOGRAPHY

Coronary angiography was performed with the Judkins or Amplatz technique and recorded on

Second Department of Internal Medicine, Oita Medical University, Oita, Japan
A Tamura
T Watanabe
Y Mikuriya
M Nasu

Correspondence to:
Dr A Tamura, Second Department of Internal Medicine, Oita Medical University, Hasama, Oita 879-55, Japan.

Accepted for publication 10 May 1995

60 mm cine film. Each pair of arteriograms was interpreted by an experienced cardiologist who was unaware of the patient's clinical data. For each lesion, an end diastolic frame from each angiogram with identical angulation that best showed the stenosis was chosen by the cardiologist. When the severity of the lesion appeared to differ on a different view, the clearest view showing the stenosis at its most severe was selected. The percent diameter stenosis of the coronary artery was measured by an automatic edge contour detection computer system (Mac Heart database system, Baxter). Coronary artery disease progression was defined as an increase of 15% or more in a percent diameter stenosis.⁸ Vessels on which angioplasty had been performed previously were excluded from the analysis. A total of 201 vessels was analysed: 62 right coronary arteries, 80 circumflex arteries, and 59 left anterior descending arteries, including 85 left main tracts.

ASSESSMENT OF FACTORS FOR CORONARY ARTERY DISEASE PROGRESSION

The following nine variables were analysed to identify factors related to disease progression without myocardial infarction: cigarette smoking (packs/day $\times$ years), body mass index, systolic blood pressure, diastolic blood pressure, fasting blood sugar, serum low density lipoprotein, serum high density lipoprotein, serum triglycerides, and serum lipoprotein(a). These variables were measured before breakfast on the morning following admission for the second angiographic study. Low density lipoprotein was estimated by the Friedewald formula.⁹

Table 1 Patient characteristics. Values are means (SD) or numbers (%)

	Progression (n = 48)	Non-progression (n = 37)	P value
Age (years)	62 (10)	65 (9)	NS
Male/female	43/5	29/8	NS
Interval (months)	38 (22)	36 (23)	NS
Previous myocardial infarct	27 (56)	25 (68)	NS
Smoking	36 (75)	24 (65)	NS
Diabetes mellitus	10 (21)	6 (16)	NS
Hypertension	24 (50)	19 (51)	NS
Hypercholesterolaemia	16 (33)	15 (41)	NS
Family history	5 (10)	3 (8)	NS
Multivessel disease	8 (17)	7 (19)	NS
Analysed vessel			
RCA	36 (75)	26 (70)	NS
LMT	48 (100)	37 (100)	NS
LAD	33 (69)	26 (70)	NS
LCX	46 (96)	34 (92)	NS
Ca blocker	46 (96)	36 (97)	NS
β Blocker	4 (8)	4 (11)	NS
Lipid lowering drugs	16 (33)	15 (41)	NS

Interval, time interval between the angiographic studies; Smoking, smoking history; Family history, family history of coronary artery disease; Multivessel disease, frequency of multivessel disease at the time of the first angiographic studies; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery.

Table 2 Summary of seven baseline variables. Values are means (SD)

	Progression (n = 48)	Non-progression (n = 37)	P value
BMI (kg/m ²)	24 (2.8)	24 (2.7)	0.90
SBP (mm Hg)	129 (19)	132 (15)	0.45
DBP (mm Hg)	73 (8.7)	74 (11)	0.73
FBS (mmol/l)	5.8 (1.7)	5.6 (1.0)	0.35
LDL (mmol/l)	3.7 (1.3)	3.4 (0.9)	0.22
TG (mmol/l)	1.5 (0.9)	1.4 (0.6)	0.74
HDL (mmol/l)	1.0 (0.3)	1.1 (0.3)	0.10

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; LDL, low density lipoprotein; TG, triglycerides; HDL, high density lipoprotein.

LIPOPROTEIN(a) ANALYSIS

Lipoprotein(a) concentrations were measured in serum using a commercially available enzyme linked immunosorbent assay kit (TintElize Lp(a) kit, Biopool). The assay, which uses polyclonal antibodies raised against purified lipoprotein(a), has been shown to be specific, sensitive, and reproducible.¹⁰

STATISTICS

Data except for lipoprotein(a) are expressed as mean (SD). Serum lipoprotein(a) levels are expressed as median values (first to third quartiles). Continuous variables except for serum lipoprotein(a) were analysed using an unpaired *t* test. A Wilcoxon test was performed to compare serum lipoprotein(a) levels. Categorical data were analysed with Fisher's exact test or the χ^2 test. Logistic regression analysis was used to identify variables related to coronary artery disease progression without new myocardial infarction. Significance was defined as a P value < 0.05.

Results

PATIENT CHARACTERISTICS

Of the 85 patients studied, 48 had coronary artery disease progression without myocardial infarction, whereas 37 had no disease progression. Disease progression in the right, left anterior descending, left circumflex, and left main coronary artery was recognised in 21, 11, 18, and one patient, respectively. There were no significant differences between the two groups in age, gender, the time interval between the angiographic studies, the incidence of multivessel disease at the time of the first angiographic studies, the distribution of analysed coronary arteries, family history of coronary artery disease, and history of previous myocardial infarction, cigarette smoking, diabetes mellitus, hypercholesterolaemia, or hypertension (table 1). In addition, there were no significant differences in the following seven baseline variables on the morning following admission for the first angiogram: body mass index, systolic blood pressure, diastolic blood pressure, fasting blood sugar, serum low density lipoprotein, serum triglycerides, and serum high density lipoprotein (table 2).

SERUM LIPOPROTEIN(a) CONCENTRATIONS

Serum lipoprotein(a) concentrations were significantly higher in the progression group than in the non-progression group [34 (14–50) mg/dl *v* 14 (9–22) mg/dl, *P* = 0.0002] (fig 1). Furthermore, 25 (52%) of the 48 patients with disease progression had a serum lipoprotein(a) concentration of 30 mg/dl or more, whereas only six (16%) of those without disease progression had a concentration of 30 mg/dl or more (*P* = 0.005).

RISK FACTORS FOR DISEASE PROGRESSION

Univariate analysis showed that serum lipoprotein(a) (*P* = 0.0002), cigarette smoking between the angiographic studies (*P* = 0.002), serum high density lipoprotein (*P* = 0.003), and serum low density lipoprotein (*P* = 0.01)

Comparison of serum lipoprotein(a) concentrations between the progression and non-progression groups

were related to coronary artery disease progression without new myocardial infarction. Multivariate analysis selected two independent factors for disease progression without myocardial infarction: serum lipoprotein(a) ($P = 0.003$) and serum high density lipoprotein ($P = 0.03$) (table 3).

Discussion

LIPOPROTEIN(a) AND ATHEROGENESIS

In a series of epidemiological studies,¹⁻⁷ a positive correlation has been shown between high serum lipoprotein(a) levels and coronary artery disease. In an immunohistochemical study, Walton *et al*¹¹ detected apoprotein(a) in the human arterial wall. However, they did not consider the possibility that lipoprotein(a) participates in atherogenesis. Rath *et al*¹² analysed biopsies taken from the ascending aorta of 107 patients undergoing aortocoronary bypass surgery and found that lipoprotein(a) accumulated in the arterial wall and that there was a positive correlation between the serum lipoprotein(a) concentration and the concentration of lipoprotein(a) in the arterial walls of the patients. Hajjar *et al*¹³ showed that lipopro-

tein(a) accumulated in the endothelium and intimal subendothelium of atherosclerotic coronary arteries derived from necropsy specimens, whereas it was not detected in normal coronary vessels from necropsy specimens. The results of these reports indicate that lipoprotein(a) participates in atherogenesis. One of the mechanisms by which lipoprotein(a) promotes atherosclerosis is thought to be through partial homology between lipoprotein(a) and plasminogen. Considering its potential role in atherogenesis, it can be surmised that healthy individuals with high serum lipoprotein(a) have a high risk of future coronary artery disease and that patients with coronary artery disease who have high serum lipoprotein(a) may have a high risk of disease progression.

Four prospective longitudinal studies¹⁴⁻¹⁷ have been performed to clarify the association between serum lipoprotein(a) and future coronary artery disease. Rosengren *et al*¹⁴ studied 776 normolipidaemic Swedish men for six years and found that 26 men with new myocardial infarction had a higher baseline serum lipoprotein(a) concentration than 109 randomly selected controls, and that men with the highest 20% of serum lipoprotein(a) concentrations (cut off point 36.5 mg/dl) had a new myocardial infarction rate more than twice that of men with the lower concentrations. Recently, the lipid research clinics coronary primary prevention trial showed that raised lipoprotein(a) is an independent risk factor for future coronary artery disease in hypercholesterolaemic white men.¹⁵ However, two other studies, the Helsinki heart study¹⁶ and the physician's health study,¹⁷ did not show any association between lipoprotein(a) levels and the risk of future myocardial infarction. Thus the predictive value of lipoprotein(a) for future myocardial infarction remains to be determined. There is only one published report¹⁸ about the relationship between serum lipoprotein(a) and angiographically assessed coronary disease progression.

THE PRESENT STUDY

In the present study, patients with coronary artery disease progression without myocardial infarction had a higher serum lipoprotein(a) concentration than those without disease progression. Furthermore, 25 of 48 patients (52%) with disease progression had a serum lipoprotein(a) concentration of 30 mg/dl or more, whereas only six (16%) of those without progression had a value of 30 mg/dl or more. Multivariate analysis selected serum lipoprotein(a) as the strongest independent factor for disease progression without new myocardial infarction. Thus our study suggests that patients with coronary artery disease and high serum lipoprotein(a) are at high risk for future coronary disease progression. These results contrast with the recent work of Marburger *et al*,¹⁸ who found that lipoprotein(a) concentrations in middle aged Caucasian men with coronary artery disease were not associated with angiographically assessed disease progression. However, in their study the time interval

Table 3 Relationship between nine variables at the second angiographic study and coronary artery disease progression without infarction. Values are means (SD) except for lipoprotein(a) (Lp(a)), where they are medians (1st-3rd quartiles)

	Progression (n = 48)	Non-progression (n = 37)	P value	
			Univariate	Multivariate
Smoking	29 (57)	1.6 (6.8)	0.002	0.07
BMI (kg/m ²)	24 (2.9)	24 (2.7)	0.36	0.65
SBP (mm Hg)	129 (18)	131 (14)	0.44	0.63
DBP (mm Hg)	72 (9.2)	74 (11)	0.61	0.71
FBS (mmol/l)	5.6 (1.6)	5.8 (1.6)	0.57	0.61
LDL (mmol/l)	3.4 (1.0)	2.9 (0.6)	0.01	0.2
TG (mmol/l)	3.2 (1.2)	3.2 (1.3)	0.81	0.32
HDL (mmol/l)	1.0 (0.3)	1.2 (0.4)	0.003	0.03
Lp(a) (mg/dl)	34 (14-50)	14 (9-22)	0.0002	0.003

Smoking, cigarette smoking between the angiographic studies (packs/day × years); BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; LDL, low density lipoprotein; TG, triglycerides; HDL, high density lipoprotein.

between the two angiographic assessments was only one year. This interval is thought to be too short for evaluating the presence or absence of coronary artery disease progression. Therefore, some of the patients with raised serum lipoprotein(a) who had no disease progression on the second angiogram may experience progression in the future.

RELATIONSHIP BETWEEN OTHER RISK FACTORS AND CORONARY ARTERY DISEASE PROGRESSION
In the present study, low levels of high density lipoprotein were also shown to be an independent factor for disease progression. Despite much evidence that low concentrations of high density lipoprotein are an important coronary risk predictor, the methods and effects of treating this condition have not been fully established. Most clinicians appear to pay less attention to low levels of high density lipoprotein than to high levels of low density lipoprotein. Efforts to increase low concentrations of high density lipoprotein in patients with coronary artery disease may be needed to prevent new myocardial infarction or disease progression. Clinical trials are needed to determine whether pharmacological intervention that specifically or at least predominantly raises high density lipoprotein is effective, especially in patients with a low high density lipoprotein but without a raised low density lipoprotein. Serum low density lipoprotein concentrations at the second angiographic study were significantly higher in the progression group than in the non-progression group. Although multivariate analysis did not show this to be an independent risk factor for progression, this does not necessarily mean that there is no association between low density lipoprotein and coronary artery disease progression. The reason is that all of our patients with hypercholesterolaemia were treated with lipid lowering drugs.

There was no difference in cigarette smoking history between the two groups. However, the number of patients continuing to smoke was significantly higher in the progression group than in the non-progression group. Univariate, but not multivariate, analysis showed that continued cigarette smoking is related to disease progression without new myocardial infarction. The importance of continued smoking as a risk factor for coronary disease progression is consistent with the findings of previous studies.¹⁹⁻²¹

STUDY LIMITATIONS

Our study has some limitations. First, as mentioned before all patients with hypercholesterolaemia received the lipid lowering drugs, pravastatin or simvastatin. A recent study²² showed that cholesterol lowering treatment can prevent angiographically assessed coronary disease progression. Therefore the use of these drugs may have affected the results of our study. However, there was no difference in the number of patients receiving lipid lowering drugs between the two groups in our study. Although nicotinic acid can decrease serum lipoprotein(a),²³ none of our patients received

this agent. Second, measurements of serum lipoprotein(a) concentrations at the time of the first coronary angiographic study were made in only about half of the patients. However, serum lipoprotein(a) is relatively stable in the same individual over time.²⁴ In our study, serum lipoprotein(a) concentrations were measured in 41 patients at the time of both the first and the second angiographic study and the values were found to be essentially the same on the both occasions. A transient increase in serum lipoprotein(a) was previously shown to be present in the acute phase of myocardial infarction and during surgical operations,²⁵ but these events did not occur in any of the patients in this study. Thus we do not believe it is a major problem that serum lipoprotein(a) was not measured in all patients at the time of the first angiographic study.

CLINICAL IMPLICATIONS

The results of the present study have led us to hypothesise that lipoprotein(a) lowering treatment may prevent disease progression in patients with coronary artery disease who have high serum lipoprotein(a). Clinical trials are desirable to determine whether patients with raised serum lipoprotein(a) will profit from its reduction.

CONCLUSIONS

This study shows that lipoprotein(a) is strongly related to the progression of coronary artery stenosis without new myocardial infarction. In patients with coronary artery disease who have high serum lipoprotein(a), not only will management of well established risk factors be necessary but lipoprotein(a) lowering treatment may also be required to prevent coronary artery disease progression.

- 1 Koster GM, Avogaro P, Cazzolato G, Marth E, Bittolo-Bon G, Qunici GB. Lipoprotein Lp(a) and the risk for myocardial infarction. *Atherosclerosis* 1981;38:51-61.
- 2 Rhoads GG, Dahlen G, Berg K, Morton NE, Dannenberg AL. Lp(a) lipoprotein as a risk factor for myocardial infarction. *JAMA* 1986;256:2540-4.
- 3 Dahlen GH, Guyton JR, Altar M, Farmer JA, Kautz JA, Gotto AM. Association of levels of lipoprotein(a), plasma lipids, and other lipoproteins with coronary artery disease documented by angiography. *Circulation* 1986;74:758-65.
- 4 Armstrong VW, Cremer P, Eberle E, Manke A, Schulze F, Wieland H, et al. The association between serum Lp(a) concentrations and angiographical assessed coronary atherosclerosis. Dependence on serum LDL levels. *Atherosclerosis* 1986;62:249-57.
- 5 Hoeffler G, Harnouncourt F, Paschke E, Mitrl W, Pfeiffer KH, Kostner GM. Lipoprotein Lp(a): a risk factor for myocardial infarction. *Arteriosclerosis* 1988;8:398-401.
- 6 Hearn JA, DeMaio SJ, Roubin GS, Hammarstrom M, Sgoutas D. Predictive value of lipoprotein(a) and other serum lipoproteins in the angiographic diagnosis of coronary heart disease. *Am J Cardiol* 1990;66:1176-80.
- 7 Seed M, Hoppichler F, Reaveley D, McCarthy S, Thompson GR, Boerwinkle E, et al. Relation of serum lipoprotein(a) concentration and apolipoprotein(a) phenotype to coronary heart disease in patients with familial hypercholesterolaemia. *N Engl J Med* 1990;322:1494-9.
- 8 Waters D, Lespérance J, Craven TE, Hudon G, Gillam LD. Advantages and limitations of serial coronary arteriography for the assessment of progression and regression of coronary atherosclerosis. *Circulation* 1993;87(suppl II):II-38-47.
- 9 Friedewald WT, Levey RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499-509.
- 10 Bradstrom A, Johnson O, Dahlen G, Ranby M. Lp(a) levels in a healthy population measured by a new enzyme linked immunoabsorbent assay. *Thromb Haemost* 1989;62:573-7.

- 11 Walton KW, Hitchens J, Magnani HN, Khan M. A study of methods of identification and estimation of Lp(a) lipoprotein and of its significance in health, hyperlipidemia and atherosclerosis. *Atherosclerosis* 1974;20:323-46.
- 12 Rath M, Niendorf A, Reblin T, Dietel M, Krebber HJ, Beisiegel U. Detection and quantification of lipoprotein(a) in the arterial wall of 107 coronary bypass patients. *Arteriosclerosis* 1989;9:579-92.
- 13 Hajjar KA, Gavish D, Breslow JL, Nachman RL. Lipoprotein(a) modulation of endothelial cell surface fibrinolysis and its potential role in atherosclerosis. *Nature* 1989;339:303-5.
- 14 Rosengren A, Wilhelmsen L, Eriksson E, Risberg B, Wedel H. Lipoprotein(a) and coronary heart disease: a prospective case-control study in a general population sample of middle aged men. *BMJ* 1990;301:1248-51.
- 15 Schaefer EJ, Lamon-Fava S, Jennifer JL, McNamara JR, Ordovas JM, Davis CE, *et al.* Lipoprotein(a) levels and risk of coronary heart disease in men. *JAMA* 1994;271:999-1003.
- 16 Jauhiainen M, Koskinen P, Ehnholm C, Frick MH, Mänttari M, Manninen V, *et al.* Lipoprotein(a) and coronary heart disease risk: a nested case-control study of the Helsinki Heart Study participants. *Atherosclerosis* 1991;89:59-67.
- 17 Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of lipoprotein(a) and the risk of myocardial infarction. *JAMA* 1993;270:2195-9.
- 18 Marburger C, Hambrecht R, Niebauer J, Schoepfentha M, Scheffler E, Hauer K, *et al.* Association between lipoprotein(a) and progression of coronary artery disease in middle-aged men. *Am J Cardiol* 1994;73:742-6.
- 19 Moise A, Lesperance J, Theroux P, Taeymans Y, Goulet C, Bourassa MG. Clinical and angiographic predictors of new total coronary occlusion in coronary artery disease: analysis of 313 nonoperated patients. *Am J Cardiol* 1984;54:1176-81.
- 20 Bemis CE, Gorlin R, Kemp HG, Herman MV. Progression of coronary artery disease. A clinical arteriographic study. *Circulation* 1973;42:455-64.
- 21 Raichlen JS, Healy B, Achuff SC, Pearson TA. Importance of risk factors in the angiographic progression of coronary artery disease. *Am J Cardiol* 1986;57:66-70.
- 22 Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987;257:3233-40.
- 23 Carlson LA, Hamsten A, Asplund A. Pronounced lowering of serum levels of lipoprotein Lp(a) in hyperlipidaemic subjects treated with nicotinic acid. *J Intern Med* 1989;226:271-6.
- 24 Albers JJ, Marcovina SM, Lodge MS. The unique lipoprotein(a): properties and immunochemical measurement. *Clin Chem* 1990;36:2019-26.
- 25 Maeda S, Abe A, Seishima M, Makino K, Noma A, Kawade M. Transient changes of serum lipoprotein(a) as an acute phase protein. *Atherosclerosis* 1989;78:145-50.