Association of lipoprotein(a) excess with early vein graft occlusions in middle-aged men undergoing coronary artery bypass surgery

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Objective: To assess the relationship of lipoprotein(a) to early vein graft occlusions in patients after coronary artery bypass grafting.

Methods: We studied 102 male patients (mean age 52.3 ± 8.6 years) with chest pain occurrence during the first year (mean time 5.3 ± 3.0 months) after surgical myocardial revascularization. Graft patency was examined by electron-beam computed tomography (n = 102) and quantitative coronary angiography (n = 31).

Results: Patients were divided into 2 groups according to graft patency data: 66 (65%) with occlusions and 36 (35%) without occlusions at follow-up. No significant differences were found between the groups concerning age, smoking, family history of coronary heart disease, previous myocardial infarction, hypertension, serum lipids, and apolipoprotein B. Lipoprotein(a) level was significantly higher in patients with occluded grafts with a median (95% confidence intervals) of 24 mg/dL (17-42 mg/dL) versus 12 mg/dL (6-24 mg/dL) in patients with patent grafts, $P < .01$. More patients with nonoccluded grafts were taking statins postoperatively: 42% versus 18% of patients with occluded grafts, $P < .05$. The sensitivity and specificity of electron-beam computed tomography in revealing vein graft occlusion was close to 100%.

Conclusion: There is an association between high lipoprotein(a) level and vein graft occlusions in middle-aged men during the first year after coronary artery bypass grafting. Use of statins is associated with a lower rate of vein graft occlusion. Electron-beam tomography could be useful for assessing graft occlusions.

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Coronary artery bypass grafting (CABG) is a key intervention in the treatment of severe symptomatic coronary heart disease (CHD). Serial angiographic studies reveal that 15% to 30% of vein grafts become stenosed within 1 year of surgery and nearly half of them are closed at 10 years.¹ Early (within the first month after CABG) graft failure is generally caused by thrombosis,² whereas intimal hyperplasia is the dominating process between 1 month and 1 year after implantation.³ Beyond 1 year after operation, atherosclerosis of vein grafts can develop.³

Lipoprotein(a) (Lp[a]) is an emerging cardiovascular risk factor. Most prospective studies have demonstrated up to a twofold risk of coronary events in healthy subjects with high Lp(a) levels.⁴ Lp(a) is a macromolecular complex of a low-density lipoprotein-like (LDL-like) particle and a unique glycoprotein, apolipoprotein(a) (apo[a]). The apo(a) molecule possesses high primary structure homology to

TABLE 1. Baseline lipids of patients and healthy men

Variable	Patients	Controls
Lp(a) median (95% CI; mg/dL)	16 (13-24)	8 (4-13)*
Lp(a) $\geq$ 30 mg/dL [n (%)]	39 (38%)	14 (18.4%)*
Total cholesterol (mmol/L)	6.4 $\pm$ 1.5	5.7 $\pm$ 1.0*
HDL-C (mmol/L)	1.0 $\pm$ 0.5	1.4 $\pm$ 0.2*
LDL-C (mmol/L)	4.3 $\pm$ 1.4	3.7 $\pm$ 0.9*
TG (mmol/L)	1.9 $\pm$ 1.4	1.9 $\pm$ 0.9

HDL-C, High-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); TG, triglycerides; TC, total cholesterol.

* $P < .01$.

the plasminogen molecule.⁵ It was shown that Lp(a) can inhibit fibrinolysis⁶ and accumulates in atherosclerotic plaques of both native coronary arteries⁷ and vein grafts.⁸

Studies investigating the relationship between vein graft lesions and Lp(a) have reported conflicting results; some have seen a correlation with late-term patency^{9,10} but others failed to find a correlation with 1-year patency¹¹ or 5-year patency¹² after operation. Given the risk of invasive angiography,¹² noninvasive assessment of vein graft patency is desirable. Previously, it was shown that cardiac electron-beam computed tomography (EBCT) had close to 100% sensitivity and specificity in detection of vein graft patency.¹³ The aim of our study was to evaluate the association of Lp(a) as well as lipid levels and traditional risk factors with the first-year occlusions of vein grafts assessed by EBCT.

Patients and Methods

We studied 102 male patients (from 28 to 68 years old, mean 52.3 $\pm$ 8.6 years) with chest pain appearance between the first and the twelfth month after myocardial revascularization by CABG (mean time after operation 5.3 $\pm$ 3.0 months). The study exclusion criteria were secondary dyslipidemia due to diabetes mellitus, dysfunction of thyroid gland, and liver or kidney failure.

The initial preoperative examination of all patients included medical history, routine clinical tests (electrocardiography [ECG], echocardiography), and coronary angiography. Before surgery, blood samples were collected from all patients and concentrations of total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) were tested immediately by specific enzymatic techniques of Boehringer Mannheim (Mannheim, Germany) on a Technicon RA-Xt analyzer (GMI, Inc, Albertville, Minn). Concentration of apolipoprotein B (apoB) was measured by a turbidimetric method with monospecific polyclonal antibodies of a goat to human LDL. LDL cholesterol (LDL-C) was calculated by the Friedewald formula¹⁴ and, after adjustment for Lp(a)-cholesterol contribution, according to G. Dahlen.¹⁵ Lp(a) concentration was determined by enzyme-linked immunosorbent assay (ELISA) using monospecific polyclonal sheep anti-human-apo(a) antibodies, as described previously.¹⁶ The intra-assay coefficient of variance has been determined to be 4.3% and 3.3% at 52 and 100 mg/dL, respectively, and the interassay coefficient of variance was 9.3% and 7.8%, respectively. Cross-reactivity with LDL and plasminogen was negligible. Regression analysis obtained 95% corre-

lation in Lp(a) determination between our version of ELISA and a commercial kit (TintElisa Lp[a] Biopool International, Umea, Sweden).

For comparison of lipid parameters, we used a control group consisting of 76 healthy male donors without a personal history of cardiovascular disease.

Postoperatively, 100 (98%) patients received aspirin and 27 (26.5%) patients took hypolipidemic therapy by statins (simvastatin, $n = 17$; lovastatin, $n = 5$; fluvastatin, $n = 5$). At follow-up, all studied patients had chest pain; bicycle ergometry was performed in 100 of them. Although the exercise test results were positive in only 33 patients, all were subjected to graft examination, which was performed by EBCT with Imatron C-150 (GE Imatron, San Francisco, Calif). Each section was made during a 0.1-second interval with a breath-hold and with ECG gating to minimize motion artifacts. The circulation time was determined with 120 mL of nonionic radiopaque preparation Omnipaque 350 (Amersham Corp, Arlington Heights, Ill) given by an automatic syringe into a cubital vein at a rate of 3.5 to 4.0 mL/s. The image processing and 3-dimensional reconstruction were carried out at a computer station MagicView 1000 (Siemens Healthcare Services, Oldbury, Bracknell, United Kingdom). The analysis of 244 vein and 92 arterial grafts was performed by 2 radiologists in a blinded manner. Also 31 patients were subjected to selective coronary and shunt angiography by the Judkins technique and a standard protocol used to define occlusions of vein graft proximal and distal anastomoses. Thus, both EBCT and coronary angiography were performed in 31 patients, with a total of 67 vein and 31 arterial grafts visualized. Occlusions of 54 vein and 3 arterial grafts were revealed by EBCT. These results were all confirmed by angiographic procedure. Thus, sensitivity and specificity of EBCT for graft occlusions in this sample was 100%.

The study was conducted in accordance to the Declaration of Helsinki and approved by the local ethics committee. All patients gave written informed consent.

Statistical analysis was performed with the MedCalc program, version 5.00.020 (developed by Mathias Tschopp). In univariate analysis, continuous variables were compared by 2-tailed t tests; the Mann-Whitney test was used for variables with non-Gaussian distribution. Discontinuous variables were compared by the χ^2 and Fisher exact tests. Multivariate analysis was done by stepwise logistic regression to obtain predictive power of risk factors in the development of vein graft occlusions. Receiver operating characteristic (ROC) curve analysis was used to obtain threshold Lp(a) for graft occlusions. Data for discontinuous variables are presented as n (%) and for continuous ones as mean $\pm$ SD or as median (95% confidence interval) for Lp(a).

Results

Of 102 patients studied, 47 (46%) had arterial hypertension, 62 (61%) had a family history of CHD, and 75 (74%) were previous or current smokers. Elevated Lp(a) ($\geq$ 30 mg/dL) was determined in 39 (38%) patients. Lipid levels of patients and healthy controls are presented in Table 1. Preoperatively, all patients had severe angina pectoris with 2 (11%) or 3 (89%) diseased coronary vessels and 56 (55%)

of them already survived myocardial infarction. The mean number of distal anastomoses was 3.7 ± 1.0 .

We performed bicycle ergometry in 100 patients. Of 33 patients with positive exercise test results, 32 had the symptoms of angina pectoris (classes I-IV according to the Canadian Cardiovascular Society) and 1 patient had silent ischemia. Atypical angina was present in 68 patients. Of 208 single vein grafts examined, 76 (36.5%) were occluded; of 19 Y-mode grafts examined, 8 (42%) were occluded; and of 17 sequential grafts examined, 8 (47%) were occluded. Occlusion of 1 or more vein grafts was demonstrated in 66 of 102 patients in our study. Patients were then evaluated according to graft status: 66 (65%) with occlusions and 36 (35%) without occlusions. Of 66 patients with occluded grafts, half had positive exercise test results. The mean number of occluded grafts in this subgroup was higher than in the other half with negative test results: 2.1 ± 1.1 versus 1.4 ± 0.7 , $t = 3.084$, 64 d.f., $P = .003$. No significant differences were found between the groups with or without occlusions concerning age, smoking, family history of CHD, previous myocardial infarction, or hypertension (Table 2). More patients with nonoccluded grafts were taking statins postoperatively: 15 of 36 (42%) versus 12 of 66 (18%) with occluded grafts ($P < .05$). Concentrations of serum total cholesterol, triglycerides, HDL-C, LDL-C, and apoB did not differ between the groups significantly, while Lp(a) level was higher in patients with occluded grafts.

Currently, the normal range of Lp(a) concentration is considered to be less than 30 mg/dL. The number of patients with occluded grafts was significantly higher if the Lp(a) level was more than 30 mg/dL: 32 of 39 (82%) compared with 34 of 63 (54%) if Lp(a) < 30 mg/dL, $P = .005$. ROC curve analysis revealed an Lp(a) threshold level of 28 mg/dL (sensitivity 49%, specificity 81%, positive predictive value 82%, negative predictive value for ≥ 1 occluded graft 46%).

Arterial graft occlusions were detected less frequently than vein graft occlusions: only 5 of 92 (5.4%) were occluded during the first year after operation. There were no differences in classic risk factors and lipid values between patients with patent and occluded arterial grafts.

Twenty-seven patients received hypolipidemic therapy with statins after operation. We compared them with 68 patients without any hypolipidemic treatment (7 patients had taken fibrates or niacin and were not considered in the analysis). Total cholesterol and LDL-C concentrations were significantly lower in the first group, whereas other lipid values did not differ (Table 3). There were more patients with patent vein grafts among those receiving statins: 15 (55%) versus 21 (28%), $P = .02$. Of 39 patients with elevated Lp(a), 10 received statins after the operation. They had a significantly lower frequency of vein graft occlusion

TABLE 2. Comparison of patients with and without occluded vein grafts

Variable	Non-occluded vein grafts	Occluded vein grafts
Patients (n)	36	66
Age (y)	51 ± 9	53 ± 9
Time after CABG (mo)	5.0 ± 2.9	5.8 ± 3.0
Current smokers	10 (26%)	20 (30%)
Previous myocardial infarction	18 (46%)	38 (57%)
Family history of CHD	21 (54%)	41 (61%)
Hypertension	16 (41%)	31 (46%)
Treatment with statins after CABG	15 (42%)	12 (18%)*
Lp(a) (mg/dL median [95% CI])	12 [6-24]	24 [17-42]†
Total cholesterol (mmol/L)	6.2 ± 1.3	6.5 ± 1.6
Triglycerides (mmol/L)	1.9 ± 1.8	1.9 ± 1.2
LDL-C (mmol/L)	4.4 ± 1.2	4.6 ± 1.5
LDL-Cc (mmol/L)	4.3 ± 1.2	4.3 ± 1.5
HDL-C (mmol/L)	1.1 ± 1.5	1.0 ± 0.4
Apolipoprotein B (mg/dL)	138 ± 56	138 ± 54

LDL-Cc, LDL-cholesterol corrected for Lp(a)-cholesterol, as was proposed by G. Dahlen.¹⁴

* $P < .05$.

† $P < .01$.

than the remaining 29 patients: 5 (50%) versus 26 (90%), $P < .05$.

In univariate rank sum correlation analysis, Lp(a) ($r = 0.230$, $P = .02$), statin therapy ($r = 0.197$, $P = .048$), and HDL-C ($r = -0.193$, $P = .07$) were related to vein graft occlusions. In a multivariate stepwise logistic regression model, the only predictors of vein graft occlusions were Lp(a) level ($P = .04$) and statin therapy ($P = .02$).

Discussion

Our study demonstrated the association between Lp(a) level and vein graft occlusions within the first year after CABG. Two other retrospective studies^{9,10} also revealed the relation of Lp(a) with vein graft lesions, but within several years after operation when there is a natural course of atherosclerosis of both native coronary arteries and grafts. In a prospective 5-year trial of 176 unselected patients with CABG, high Lp(a) concentration tended to be associated with obstructive changes in vein grafts, whereas mean levels of serum lipids and lipoproteins, other traditional risk factors for atherosclerosis, and subcutaneous fatty acid composition were similar in patients with and without graft occlusion.¹⁷ Other prospective trials did not reveal an association of Lp(a) level with clinical and angiographic outcome 5 years after CABG.^{12,18}

Our main finding is the demonstration of the relationship of Lp(a) excess with vein graft occlusions in the first months after operation when the processes of thrombosis and intimal hyperplasia are prevailing.³ This could be explained by prothrombotic properties of the Lp(a) particle.⁶ In vitro studies have shown that Lp(a) stimulates smooth muscle

TABLE 3. Lipid profile and treatment with statins after operation

Variable	Without statins (n = 68)	With statins (n = 27)	P
Lp(a) (mg/dL median [95% CI])	23 [15-33]	18 [10-36]	.5
Total cholesterol (mmol/L baseline)	6.6 ± 1.5	7.0 ± 1.3	.2
Total cholesterol (mmol/L at follow-up)	6.6 ± 1.5	5.6 ± 1.4†	<.01
Triglycerides (mmol/L baseline)	1.8 ± 1.8	2.0 ± 1.8	.6
Triglycerides (mmol/L at follow-up)	2.1 ± 1.6	1.4 ± 1.1*	.02
LDL-C (mmol/L)	4.7 ± 1.4	3.9 ± 1.3	.01
LDL-Cc (mmol/L)	4.5 ± 1.6	3.5 ± 1.5	.006
HDL-C (mmol/L)	1.0 ± 0.4	1.1 ± 0.6	.3
Apolipoprotein B (mg/dL)	140 ± 55	131 ± 46	.5

LDL-Cc, LDL-cholesterol corrected for Lp(a)-cholesterol, as was proposed by G. Dahlen.¹⁴

* $P < .05$; † $P < .01$, versus baseline levels of total cholesterol and triglycerides.

cell proliferation, may compete for fibrin binding, interacts with cell plasminogen receptor, and accumulates in thrombi.^{19,20} Therefore, Lp(a) may interfere with fibrinolysis and support a prothrombotic state. However, a prospective study of 610 patients undergoing CABG did not find an effect of Lp(a) level on graft patency at 1 year after CABG.¹¹ Shunt angiography was performed in 95% of patients at a mean 12.1 ± 1.5 months after surgery. One or more occlusions of vein graft were revealed in almost half of the patients. The explanation of the conflict between this and our studies could lie in differences of patient cohorts; the first one was unselected and consisted of both men (87%) and women, whereas our patients were only symptomatic middle-aged men. Thus, possible reasons for this disagreement could be the difference in age, sex, and the combination of risk factors in studied groups. The high rate of graft occlusion in our study is explained by the inclusion of patients with symptoms of typical or atypical angina, though two thirds of them did not have signs of ischemia on ECG. Probably, stress-echocardiography could help to obtain ischemic signs in this subgroup, but this method was not included in the study protocol.

Some studies examined the role of hemostatic factors in prognosis after CABG. In one of these studies, angiography performed 10 days postoperatively showed graft occlusion in 23% of 82 patients. Patients with graft occlusion had significantly ($P < .001$) higher preoperative plasminogen activator inhibitor activity than patients without occlusion.²¹ These results suggest that increased plasminogen activator inhibitor activity might have a positive predictive value for early thrombosis in patients undergoing CABG. Preoperative and postoperative determinations (performed on the first, third, and sixth postoperative days) of hemostatic factors were performed in 100 men who had undergone elective CABG for stable angina pectoris.²² Occlusion of one or more vein grafts within 3 months of surgery occurred in 23 of them. The percentage increase in plasma plasminogen activator inhibitor-1 activity and fibrinogen levels

within the first postoperative week were significantly ($P < .05$) higher in patients who subsequently were found to have vein graft occlusion.²² We propose that in patients with high Lp(a) level there is an increased risk of thrombotic graft occlusion due to concurrent inhibition of plasminogen by Lp(a) particles.

We have determined that therapy with statins is associated with a lower frequency of graft occlusion even in the first year after CABG. In the Post-CABG trial, the investigators showed that statin therapy reduced the progression of vein graft disease, the incidence of vein graft occlusion, and the need for further revascularization.²³ This large study was started at 1 to 11 years after CABG and angiography was repeated an average of 4.3 years after baseline. The hypolipidemic therapy in our study was begun soon after operation and, though it was not randomized, the use of statins was associated with significantly better graft functioning in first months after operation. The reduction of blood thrombogenicity and endothelial dysfunction,²⁴ as well as anti-inflammatory effect,^{25,26} may be mechanisms by which statins improve graft function and patency much earlier than the retarding of atherosclerosis through hypolipidemic activity.

We found EBCT to have high sensitivity for graft occlusion. Previously, it was shown that evaluation for hemodynamically relevant stenosis was possible in 84% of cases (36 of 43 patent grafts) and yielded a sensitivity of 100% (5 of 5 high-grade stenoses correctly detected) and a specificity of 97%.¹³ We performed a substudy to compare EBCT and coronary angiography and obtained comparable accuracy in the revelation of graft occlusion. Therefore, we believe that EBCT should be used more widely to assess the condition of coronary grafts.

In conclusion, we found a significant association between elevated Lp(a) level and vein graft occlusion in middle-aged men in their first postoperative year. Patients not receiving statins and with Lp(a) excess had the highest rate of vein graft occlusion (90%). It would be useful to

measure Lp(a) concentration before surgery because patients with Lp(a) of 30 mg/dL or greater are at higher risk of subsequent vein graft lesions. Currently, there is no drug therapy available to lower Lp(a). Specific extracorporeal Lp(a) removal by Lp(a) apheresis, a procedure first designed and performed by our group, may retard progression of atherosclerosis in patients with selective Lp(a) elevation.^{27,28} Taking into consideration the data that cardiovascular risk associated with high Lp(a) level is markedly enhanced when LDL-C is also elevated,²⁹ soon after CABG all patients with both higher and normal Lp(a) levels in association with elevated LDL should receive aggressive hypolipidemic therapy, with the aim of avoiding fast progression of atherosclerosis in the bypasses. There is a need for future work in the investigation of the pathophysiologic role of Lp(a) in atherothrombosis and, furthermore, large prospective clinical trials could provide clarity as to the use of measuring Lp(a) level.

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