Original paper

Plasma lipoprotein(a) levels in patients with slow coronary flow

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Abstract

Introduction: Slow coronary flow (SCF) is a microvascular disorder characterized by delayed opacification of coronary vessels with normal coronary angiogram. It may be due to endothelial dysfunction and diffuse atherosclerosis. Lipoprotein(a) [Lp(a)] is related to cardiovascular events. Plasma Lp(a) levels have not been studied previously in SCF patients.

Aim: We investigated plasma Lp(a) and fibrinogen levels, and their relation to coronary flow rate in patients with SCF.

Material and methods: This cross-sectional study included 50 patients with SCF and 30 age- and sex-matched controls who had normal coronary arteries and normal flow. Coronary flow rates of patients and controls were counted with the thrombolysis in myocardial infarction (TIMI) frame count. Plasma Lp(a) and fibrinogen levels were measured in SCF patients and controls, with routine biochemical tests.

Results: There were no significant differences between the two groups with respect to plasma Lp(a) (21 mg/dl vs. 14 mg/dl, $p = 0.11$) and fibrinogen (278 mg/dl vs. 291 mg/dl, $p = 0.48$) levels. The TIMI frame count was not correlated with plasma Lp(a) ($r = 0.13$, $p = 0.25$) or fibrinogen ($r = -0.14$, $p = 0.28$) levels.

Conclusions: Our results show that there is no significant association between SCF and Lp(a) and fibrinogen levels.

Key words: lipoprotein(a), fibrinogen, slow coronary flow, cardiovascular disease.

Introduction

Slow coronary flow (SCF) is defined as late opacification in the epicardial coronary arteries without significant stenosis based on the coronary images [1]. Although the pathophysiological mechanisms of SCF remain uncertain, there are several hypotheses suggested [2]. Endothelial dysfunction and diffuse atherosclerosis may lead to SCF. Based on this hypothesis, SCF may be a form of early phase of atherosclerosis [3].

Lipoprotein(a) [Lp(a)] is a cholesterol ester-rich lipoprotein composed of a low-density lipoprotein (LDL) particle and a large glycoprotein, apolipoprotein(a). There is a debate on the association of Lp(a) with coronary artery disease (CAD). Some studies have reported a significant association [4–8], but others have not [9, 10]. Also, plasma fibrinogen levels have been shown to be correlated with Lp(a) in patients with and without CAD [11].

Aim

To our knowledge, there is no study about plasma Lp(a) levels in patients with SCF. Therefore, we aimed to evaluate plasma Lp(a) levels in patients with SCF and factors associated with the thrombolysis in myocardial infarction (TIMI) frame count.

Material and methods

One hundred and nineteen consecutive patients with SCF were evaluated. Of all of them, 69 patients were excluded due to hypertension ($n = 25$), stenotic lesion $\geq 30\%$ ($n = 20$), diabetes mellitus ($n = 13$), coronary artery ectasia ($n = 9$), hypothyroidism ($n = 1$) and systemic disease ($n = 1$). The remaining 50 patients created the SCF group. The age- and gender-matched control group was composed of 30 patients with normal coronary arteries and normal coronary flow. The indication for coronary

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angiography was either the presence of typical angina or positive or equivocal results of noninvasive screening tests for myocardial ischemia in both groups.

Each patient was questioned about major cardiovascular risk factors including family history of CAD, current smoking status, diabetes mellitus, hypertension, hyperlipidemia and obesity. Family history of CAD was defined as CAD in first-grade male relatives before 55 years and in female relatives before 65 years of age. Hypertension was defined as systolic pressure > 140 mm Hg and/or diastolic pressure > 90 mm Hg or being on antihypertensive medications. Hypercholesterolemia was defined as fasting total cholesterol level > 200 mg/dl or being on lipid-lowering agents. Diabetes mellitus was defined as a fasting blood glucose level > 126 mg/dl or current use of an anti-diabetic agent. Obesity was defined as body mass index > 30 kg/m^2. Patients who were smoking before hospitalization were considered as smokers.

Non-inclusion criteria were prior myocardial infarction, acute coronary syndromes, moderate to severe valvular heart disease, New York Heart Association (NYHA) class II–IV chronic heart failure, acute heart failure, hypertension, diabetes mellitus, coronary ectasia, peripheral vascular disease, connective tissue disease, renal or hepatic dysfunction, hematological disorders, females taking oral contraceptive pills or hormone replacement therapy, familial hypercholesterolemia, hypothyroidism, including subclinical hypothyroidism, pregnancy, chronic obstructive pulmonary disease or cor pulmonale, history of malignancy, acute or chronic infection, stroke, taking cholesterol-lowering treatment within 4 weeks, use of any drug affecting Lp(a) levels including oestrogens, androgens, anabolic steroids and ω-3 polyunsaturated fatty acids, and regular alcohol use or alcohol use within 48 h. Patients with SCF who had ≥ 30% diameter stenosis of major coronary arteries were also excluded from the study. The study was approved by the institutional review board, and informed consent was obtained from all the patients.

Coronary angiography

Selective coronary angiography was performed via a transfemoral approach with the Judkins technique in multiple projections without the use of nitroglycerin. We used iopamidol (Iopamiro) as a contrast agent. Coronary arteries were demonstrated with at least four views of the left coronary system using 6 Fr left coronary catheters and two views of the right coronary artery using 6 Fr right coronary catheters at the rate of 15 fps in the same cardiac catheterization laboratory. Coronary blood flow was measured quantitatively using the TIMI frame count. Initial frame count is defined as the frame in which concentrated dye occupies the full width of the proximal coronary artery lumen, touching both borders of the lumen, and forward motion down the artery. The final frame is designated when the leading edge of the contrast column initially arrives at the distal end. Distal end was defined as the distal bifurcation for the left anterior descending artery (LAD), the distal bifurcation of the segment with the longest total distance for the circumflex artery (Cx), and the first branch of the posterolateral artery for the right coronary artery (RCA). The LAD coronary artery is usually longer than the other major coronary arteries; the TIMI frame count for this vessel is often higher. To obtain the corrected TIMI frame count for the LAD coronary artery, the TIMI frame count was divided by 1.7 [12]. The mean TIMI frame count for each patient and control subject was calculated by adding the TIMI frame count for LAD, Cx and RCA and then dividing the obtained value by three. Due to different durations required for normal visualization of coronary arteries, the corrected cutoff values were 36.28 ±2.6 frames for LAD, 22.28 ±4.1 frames for Cx, and 20.48 ±3 frames for RCA, as has been reported earlier in the literature [12]. All participants with a TIMI frame count greater than two standard deviations of the previously published range for a particular vessel were considered to have SCF. Any values obtained above these thresholds in 1 of 3 coronary arteries (not all 3) were considered to be SCF in our study. Coronary angiograms and TIMI frame counts were analyzed by two experienced interventional cardiologists blinded to the clinical status and laboratory measurements of the subjects.

Measurements of plasma lipoprotein(a)

Blood samples were taken in the morning of the examination after overnight fasting and drawn into heparinized tubes for biochemical analysis. For the measurement of Lp(a), plasma samples were stored frozen at ≤ –30°C after immediate centrifugation (4000 × g for 10 min at 4°C). Whole blood count and routine biochemical tests were performed with an autoanalyzer (Aeroset, Abbott, Abbott Park, IL, USA).

Plasma Lp(a) levels were measured as batch with the microenzyme-linked immunosorbent assay (ELISA) method using a total human Lp(a) ELISA assay kit (Immunospec corporation, California, US). All plasma samples for Lp(a) were measured by the same assay and single assay. Results were expressed as mg/dl.

Statistical analysis

Data were analyzed with the SPSS software version 11.0 for Windows. Continuous variables were reported as mean ± standard deviation and categorical variables as percentages. To compare continuous variables, Student *t* test or Mann-Whitney *U* test was used where appropriate. Categorical variables were compared with χ^2 test. Mann-Whitney *U* test was used for comparing plasma Lp(a) and fibrinogen levels. Spearman correlation analysis was performed for the analysis of factors correlated

with mean TIMI frame count. Statistical significance was defined as $p < 0.05$.

Results

Demographic and clinical characteristics of the SCF and control group are presented in Table 1. There were no statistically significant differences between the two groups with respect to body mass index, systolic and diastolic blood pressures, heart rate and risk factors for CAD such as hyperlipidemia, cigarette smoking, family history and obesity (all $p > 0.05$). The use of aspirin was significantly higher in the SCF group than the control group (50% vs. 17%, $p = 0.004$) but there were no significant differences between the two groups with respect to the use of other medications (all $p > 0.05$).

Laboratory and angiographic characteristics of SCF patients and controls are presented in Table 2. The groups were similar in terms of creatinine, total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, hemoglobin, hematocrit, white blood cell count and platelet count (all $p > 0.05$). Fasting glucose was significantly higher in SCF than controls ($p = 0.01$). Inversely, high-density lipoprotein (HDL) cholesterol was significantly lower in SCF ($p = 0.03$).

There were no statistically significant differences between the two groups with respect to plasma Lp(a)

Table 1. Demographic and clinical characteristics of patients with SCF and control group

Variable	SCF group ($n = 50$)	Control group ($n = 30$)	Value of p
Age [years]	53.0 ±9.1	51.1 ±8.1	0.36
Gender (male/female)	27/23	15/15	0.73
Hyperlipidemia	14 (28%)	4 (13%)	0.13
Smoking	10 (20%)	6 (20%)	0.99
Family history of CAD	10 (20%)	9 (30%)	0.31
Obesity	21 (42%)	8 (27%)	0.17
Body mass index [kg/m²]	29.4 ±4.1	27.7 ±4.0	0.12
Systolic blood pressure [mm Hg]	119.1 ±18.5	122.0 ±8.7	0.76
Diastolic blood pressure [mm Hg]	75.2 ±9.0	765 ±6.8	0.83
Heart rate [beats/min]	71.0 ±7.3	70.6 ±6.7	0.94

SCF – slow coronary flow, CAD – coronary artery disease

Table 2. Laboratory and angiographic characteristics of patients with SCF and control group

Variable	SCF group ($n = 50$)	Control group ($n = 30$)	Value of p
Fasting glucose [mg/dl]	100.7 ±16.7	91.3 ±12.5	0.01
Creatinine [mg/dl]	0.92 ±0.15	0.88 ±0.15	0.26
Total cholesterol [mg/dl]	190.3 ±33.1	190.6 ±45.4	0.85
Triglycerides [mg/dl]	150.6 ±67.3	130.8 ±52.5	0.25
LDL cholesterol [mg/dl]	112.4 ±28.2	109.4 ±37.9	0.47
HDL cholesterol [mg/dl]	47.5 ±12.5	54.56 ±15.1	0.03
Hemoglobin [g/dl]	14.4 ±1.39	14.3 ±1.42	0.89
Hematocrit [%]	42.0 ±3.7	40.8 ±4.4	0.10
White blood cells [× 10⁹/l]	7.5 ±2.1	7.1 ±2.2	0.33
Platelet count [× 10⁹/l]	257.5 ±62.0	253.6 ±76.8	0.95
TIMI frame count			
cLAD	32.2 ±8.7	15.7 ±1.8	< 0.001
Cx	27.0 ±9.0	18.5 ±2.9	< 0.001
RCA	20.7 ±4.6	16.5 ±2.6	< 0.001
Mean TFC	26.8 ±5.5	16.9 ±2.0	< 0.001
Fibrinogen [mg/dl]*	278 (240–319)	291 (250–342)	0.48
Lipoprotein(a) [mg/dl]*	21 (14–32)	14 (6–35)	0.11

*Median (interquartile range). Data presented as mean ± SD
SCF – slow coronary flow, LDL cholesterol – low-density lipoprotein cholesterol, HDL cholesterol – high-density lipoprotein cholesterol, TIMI – thrombolysis in myocardial infarction, c – corrected TIMI frame count, LAD – left anterior descending artery, Cx – circumflex artery, RCA – right coronary artery, TFC – TIMI frame count

(21 vs. 14 mg/dl, $p = 0.11$) or fibrinogen (278 vs. 291 mg/dl, $p = 0.48$) levels. The TIMI frame count was not correlated with plasma Lp(a) ($r = 0.13$, $p = 0.25$) or fibrinogen ($r = -0.14$, $p = 0.28$) levels. Similarly, plasma Lp(a) levels were not correlated with fibrinogen ($r = 0.31$, $p = 0.053$) in the SCF group.

Discussion

In the present study, we demonstrated that there was no significant association between Lp(a) and fibrinogen levels, and SCF. To the best of our knowledge, this is first study investigating plasma Lp(a) levels in patients with SCF.

Diffuse atherosclerosis may play an important role in the pathogenesis of SCF [3]. It has been shown that plasma nitric oxide (NO) levels were significantly lower in patients with SCF than in those with normal coronary flow and were inversely correlated with TIMI frame counts [13]. Several studies have shown significant changes in plasma levels of oxidative stress parameters in patients with SCF compared to healthy individuals [14–16]. Lipoprotein(a) can be an independent risk factor for atherogenic disease [4–8] and also inactivate NO through superoxide anion production and interfere with the stimulation of NO synthase on the endothelium [17]. Thus, it is likely that there may be an association between Lp(a) and SCF according to the results of the studies mentioned above.

Lipoprotein(a) can be related to impaired endothelium-dependent dilatation [18, 19]. Previous studies have reported that subjects with increased Lp(a) levels (250 mg/l and 300 mg/l) had reduced acetylcholine-induced coronary vasodilation [19, 20] and that increased Lp(a) levels may be associated with coronary endothelial dysfunction. Similarly, it has been shown that healthy young subjects with increased Lp(a) levels had reduced myocardial vasoreactivity [21].

Several studies have shown that there is an association between plasma Lp(a) levels and CAD [4–8]. Moreover, it is likely that there can be a causal association between elevated Lp(a) levels and increased risk of myocardial infarction [8]. A recent large-scale study demonstrated that Lp(a) levels were positively associated with cardiovascular events [22]. Similarly, a meta-analysis including 67 prospective studies showed a clear association between elevated Lp(a) levels and increased risk of CAD [23].

In the present study, coronary blood flow was measured quantitatively using the TIMI frame count, and potential confounding factors that affect Lp(a) such as hypertension [24–26] and diabetes mellitus [25, 27] were eliminated. We examined the association between Lp(a) and coronary blood flow when atherosclerotic lesions were not recognizable by angiography and there were no significant results. Thus, the present study is the first one investigating the association between Lp(a) and coronary blood flow.

Despite studies supporting Lp(a) concentration as a CAD risk factor, the actual mechanisms linking Lp(a) to atherogenesis remain undefined. Two studies have shown that there was no association between Lp(a) and atherosclerosis [9, 10]. Also, when SCF is accepted as a form of early phase of atherosclerosis, our results indicate that there was no association between Lp(a) and atherosclerosis, consistent with the findings of previous studies. In a previous study, it was found that Lp(a) levels were not associated with risk for CAD in Turkish people [28]. Similarly, a recent study showed that Lp(a) levels were not associated with change in carotid intima-media thickness or brachial flow-mediated dilation [10].

A correlation of circulating fibrinogen with Lp(a) levels was found in patients with primary dyslipidemia [29]. Previous clinical studies showed that patients with elevated serum Lp(a) levels had a significantly increased cardiovascular disease risk together with high fibrinogen levels [30–32]. In this study, there was a weak correlation between Lp(a) and fibrinogen levels, but plasma fibrinogen levels were comparable in the two groups.

Aspirin can be used in treatment of SCF [33]. It has been demonstrated that mean platelet volume significantly increased in patients with SCF, altered platelet reactivity and aggregation which may require effective anti-platelet therapy [34]. As far as we are aware, there is no study investigating the effects of aspirin in SCF. A recent study showed that aspirin did not improve brachial flow-mediated dilatation (FMD), an index of endothelial function in patients with SCF. However, patients treated with aspirin were free of angina after treatment of SCF [35]. In this study, use of aspirin was significantly higher in the SCF group than the control group. In some previous studies, it was observed that aspirin decreased plasma Lp(a) levels [36–38].

Study limitations – the sample size of this study is small and thus significant findings might not have been obtained. The diagnosis of normal coronary arteries was based on contrast angiograms of the vessel lumen, which underestimate the presence of atherosclerotic plaques. The use of aspirin was significantly higher in the SCF group than the control group.

Conclusions

This observational study shows that there is no significant association between SCF and Lp(a) and fibrinogen levels. However, further large studies are required to determine the pathophysiological and clinical significance of Lp(a) in patients with SCF.

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