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Does Lipoprotein(a) Impair Endothelial Function?

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Objectives. **This study was undertaken to test the hypothesis that lipoprotein(a) [Lp(a)] impairs endothelial function.**

Background. **Elevated Lp(a) plasma levels have been demonstrated to be associated with an increased risk of coronary heart disease. In atherosclerosis, endothelial dysfunction is known to be an early indicator of vascular changes. However, the effect of Lp(a) on nitric oxide (NO)-dependent vasodilator response has not yet been determined. We therefore examined the influence of Lp(a) on basal and stimulated NO-mediated vasodilator response in the forearm vascular bed.**

Methods. **Strain gauge plethysmography was used to measure changes in forearm blood flow produced by intraarterial infusion of increasing doses of acetylcholine (3, 12, 24 and 48 μg/min), sodium nitroprusside (200, 800 and 3,200 ng/min) and N-monomethyl L-arginine (L-NMMA) (1, 2 and 4 μmol/min) in 57 white subjects (mean age ± SD 37 ± 14 years). Lp(a) plasma concentrations were determined by rocket immunoelectrophoresis.**

Results. **Endothelium-dependent vasodilation tested by intraarterial acetylcholine and endothelium-independent vascular relaxation tested by intraarterial sodium nitroprusside were not correlated with Lp(a). Similarly, no significant differences in forearm blood flow changes were observed when patients were classified into tertiles according to their individual Lp(a) concentration. In contrast, changes in forearm blood flow after intraarterial L-NMMA indicating basal production and release of NO differed significantly among tertiles. Patients in the highest Lp(a) tertile (49.2 ± 20.3 mg/dl) had a much greater vasoconstrictive response to L-NMMA than patients in the lowest Lp(a) tertile (4.8 ± 2.5 mg/dl): 2 μmol/min of L-NMMA, −23.6 ± 22.5% vs. −10.4 ± 9.1% ($p < 0.02$); 4 μmol/min of L-NMMA, −27.8 ± 10.3% vs. −17.6 ± 9.9% ($p < 0.03$). Lp(a) plasma level consistently correlated negatively with the forearm blood flow responses to 4 μmol/min of intraarterial L-NMMA ($r = −0.38$, $p < 0.01$). Multiple stepwise regression analysis of variables, including total and high and low density lipoprotein cholesterol, further confirmed that plasma Lp(a) remained a significant independent determinant of forearm blood flow changes in response to L-NMMA ($p < 0.02$).**

Conclusions. **The endothelium-dependent vasoconstrictive response to L-NMMA was enhanced in subjects with relatively high Lp(a) plasma levels, suggesting an increased basal production and release of NO. This response seemed to reflect a compensatory mechanism of the endothelium to yet unknown Lp(a)-induced atherosclerotic effects.**

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In previous prospective studies (1–4), elevated lipoprotein(a) [Lp(a)] plasma levels have been shown to predict cardiovascular disease. In addition to established cardiovascular risk factors, elevated serum levels of Lp(a) indicate an increased risk for major coronary events (5). Well recognized atherosclerotic risk factors such as smoking, high blood pressure, diabetes mellitus and hypercholesterolemia, are known (6–9) to impair endothelium-dependent vasodilation, even if no clinical or angiographic signs of atherosclerosis are present. For example, elevated low density lipoprotein (LDL) cholesterol levels attenuated the vasodilator response to acetylcholine in coronary arteries that appeared normal on coronary angiograms (6,10). Furthermore, elevated high density lipoprotein (HDL) levels were shown (11) to ameliorate abnormal vasoconstriction in early atherosclerosis. Similar interactions were demonstrated between Lp(a) levels and cerebrovascular disease (12,13). An elevated Lp(a) plasma level in hypercholesterolemic patients was found to be an independent risk factor for thickening of common carotid arteries (14), which in turn is associated with an increased risk of cerebrovascular events. Although Lp(a) concentration is mainly genetically determined, it was suggested that plasma concentrations might be altered by conditions such as renal disease (15), liver disease (16), age, gender, body mass index and hemostatic factors (17). Controversially, other investigators (18) did not find any relation between Lp(a) and other well known cardiovascular risk factors. It is also poorly defined which Lp(a) concentration represents the threshold for the development of atherosclerosis and associated conditions. Most previous studies (1–5) reported that the atherogenetic threshold of plasma Lp(a) levels in humans is between 20 and 30 mg/dl.

The exact pathogenetic mechanism by which elevated Lp(a)

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Abbreviations and Acronyms

ANOVA = analysis of variance
HDL = high density lipoprotein
LDL = low density lipoprotein
Lp(a) = lipoprotein(a)
L-NMMA = N-monomethyl L-arginine
NO = nitric oxide

plasma levels contribute to the development of atherosclerosis is not completely understood. Experimental studies (19) suggest that some components of Lp(a) can enhance lipid deposition in vessel walls, thereby interfering with fibrinolysis, smooth muscle cell activity and endothelial function. In vivo studies (6,20,21) revealed increasing evidence that endothelium dysfunction assessed by administration of endothelium-dependent vasoactive substances, such as acetylcholine and N-monomethyl L-arginine (L-NMMA), may precede and promote the process of atherosclerosis in humans. Therefore, the assessment of endothelial function is helpful in detecting stages of early vascular structural changes, even before atherosclerotic lesions of the coronary arteries can be angiographically detected.

To our knowledge, there have been no reports on the effect of elevated Lp(a) plasma levels on endothelium function in the human vasculature. We therefore conducted this study in middle-aged white subjects to test the hypothesis that elevated Lp(a) plasma levels considered as an independent risk factor for atherosclerosis impair endothelium function. We assessed vasoreactive response to endothelium-dependent (acetylcholine, L-NMMA) and endothelium-independent (sodium nitroprusside) vasoactive substances. In a first approach we used the human forearm vasculature because of its easy accessibility, lack of adverse and potentially lethal complications (as observed in the coronary arteries) and its close relation to other human vasculature, as reported earlier (22).

Methods

Study cohort. According to a program for the prevention of cardiovascular disease initiated by the University of Erlangen-Nuremberg, ~400 white male and female persons from the area of Nuremberg were screened for hypercholesterolemia and asked to participate in a scientific study regardless of their cholesterol level. If they agreed to participate, subjects were consecutively enrolled and asked to refer to our outpatient clinic of the Department of Medicine, University of Erlangen-Nuremberg. A total of 57 middle-aged white subjects (33 male and 24 female, mean age ± SD 37 ± 14 years) fulfilled all inclusion criteria such as no clinical evidence of atherosclerosis or any cardiovascular disease. No participant followed any lipid-lowering dietary guideline, was receiving antilipemic therapy or had diabetes or secondary hyperlipidemia. A routine clinical evaluation and a 12-lead electrocardiogram performed in all subjects yielded no evidence of pathologic findings. The study protocol was approved by the ethics committee of the University of Erlangen-Nuremberg and all participants gave written informed consent before the study.

Study protocol. Throughout the study period, subjects rested in a supine position in a quiet room with a controlled temperature of 22°C. An intraarterial line was inserted under strict aseptic conditions into the brachial artery of the left arm with use of the Seldinger technique. After brachial cannulation, patients rested for 30 min before the study was begun. The forearm vascular response to vasoactive agents was assessed by venous occlusion plethysmography with a sealed alloy-filled, double-stranded strain gauge (EC 5R Plethysmograph). Hand blood flow was excluded by means of a wrist cuff inflated to 200 mm Hg during the measurement phase. Venous occlusion pressure on the arm was 50 mm Hg. Drugs were infused at a rate of 2 ml/min by an infusion pump. Three substances were administered. To assess endothelium-dependent vasodilation, intraarterial acetylcholine was infused at sequential doses of 3, 12, 24 and 48 μg/min. Sodium nitroprusside was administered intraarterially (at doses of 200, 800 and 3,200 ng/min) to test endothelium-independent vasorelaxation and L-NMMA was administered at doses of 1, 2 and 4 μmol/min to test the basal production and release of nitric oxide. Each dose was infused for 5 min. Before each intervention with a different drug, forearm blood flow was allowed to return to rest levels for 15 min. Baseline forearm blood flow was obtained from an average of three measurements. Forearm blood flow responses were measured at the end of each infusion period as the average of three consecutive steady state measurements. No significant changes in blood pressure or heart rate were observed during drug administration, thus verifying the local application of each drug and excluding systemic effects of the vasoactive substances.

Measurements of Lp(a) and other lipids. Plasma Lp(a) levels were determined by using a commercially available rocket immunoelectrophoresis (Immuno AG, Vienna). Apolipoproteins A and B were measured by nephelometry (Behring, Marburg). Total cholesterol, triglycerides and high density lipoprotein (HDL) cholesterol were measured by an enzymatic technique according to the specifications of the Lipid Research Clinics Program (23). LDL cholesterol was calculated by the formula of Friedewald et al. (24).

Statistical analysis. Vascular reactivity data are expressed as the percent change from the corresponding baseline values. Patients were arbitrarily classified into tertiles according to their Lp(a) plasma concentration. Analysis of variance (ANOVA) with the Bonferroni correction was applied to test differences among tertiles. Linear regression analysis was used to evaluate the effect of Lp(a) and other variables on forearm blood flow changes. Multiple stepwise regression analysis was then conducted to analyze which of the univariate variables were independent determinants of the vasoreactive response to the different drugs infused. The variable with the highest partial correlation was entered at each step until no variable remained with an F value ≥2. Changes in forearm blood flow

Table 1. Characteristics of the 57 Study Patients

	Mean ± SD
Age (yr)	36.8 ± 14.3
Weight (kg)	72.2 ± 10.8
Height (m)	1.73 ± 0.08
Body mass index (kg/m^2)	23.9 ± 3.1
Systolic BP (mm Hg)	122 ± 15
Diastolic BP (mm Hg)	78 ± 11
Total cholesterol (mg/dl)	237 ± 75
LDL cholesterol (mg/dl)	213 ± 59
HDL cholesterol (mg/dl)	65 ± 20
Triglycerides (mg/dl)	132 ± 75
Lp(a) (mg/dl)	22.3 ± 22.7

BP = blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein; Lp(a) = lipoprotein(a).

are reported as mean value ± SE; all other values as mean value ± SD. Two-sided p values are given throughout the text.

Results

Patient characteristics. Clinical characteristics of the total study group are given in Table 1. All 57 subjects were normotensive, and none was taking any specific cardiovascular medication. No participant had a history of diabetes. The mean Lp(a) plasma level was 22.30 ± 22.69 mg/dl (4.8 ± 2.5, 13.0 ± 3.0 and 49.2 ± 20.3 mg/dl in the lower, middle and upper tertile, respectively). Age; body mass index; blood pressure; and total, HDL and LDL cholesterol did not differ among tertiles (Table 2). Six of the 57 subjects were smokers with a daily cigarette consumption of 2 to 6 cigarettes/day. Three smokers were in the lower tertile, one in the middle and two in the upper tertile; mean cigarette consumption did not differ among tertiles. None of the 24 female subjects was on a regimen of oral contraceptives or transdermal estrogen substitution.

Table 2. Characteristics of Subjects Classified by Lipoprotein(a) Plasma Level Tertile*

Lp(a)	Lower Tertile (n = 19)	Middle Tertile (n = 19)	Upper Tertile (n = 19)
Age (yr)	31.8 ± 11.4	41.7 ± 15.8	36.8 ± 14.5
Weight (kg)	73.0 ± 11.0	73.0 ± 9.0	70.8 ± 12.4
Height (m)	1.75 ± 0.09	1.73 ± 0.09	1.72 ± 0.05
Body mass index (kg/m^2)	23.7 ± 3.3	24.5 ± 3.0	23.8 ± 3.2
Systolic BP (mm Hg)	123 ± 14	124 ± 14	122 ± 18
Diastolic BP (mm Hg)	78 ± 8	77 ± 11	77 ± 13
Total cholesterol (mg/dl)	224 ± 86	256 ± 74	230 ± 64
LDL cholesterol (mg/dl)	141 ± 80	167 ± 71	135 ± 56
HDL cholesterol (mg/dl)	60 ± 15	61 ± 15	74 ± 26
Triglycerides (mg/dl)	113 ± 78	144 ± 79	105 ± 56

*Analysis of variance showed no significant differences among tertiles for any of the variables shown. Data are presented as mean value ± SD. Lower Tertile = lipoprotein(a) [Lp(a)] <10 mg/dl (average: 4.8 ± 2.5); Middle Tertile = Lp(a) ≥10 and ≤20 mg/dl (average: 13.0 ± 3.0); Upper Tertile = Lp(a) >20 mg/dl (average: 49.2 ± 20.3). Abbreviations as in Table 1.

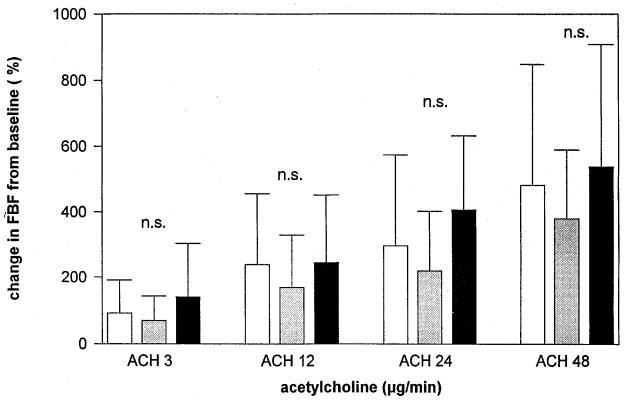


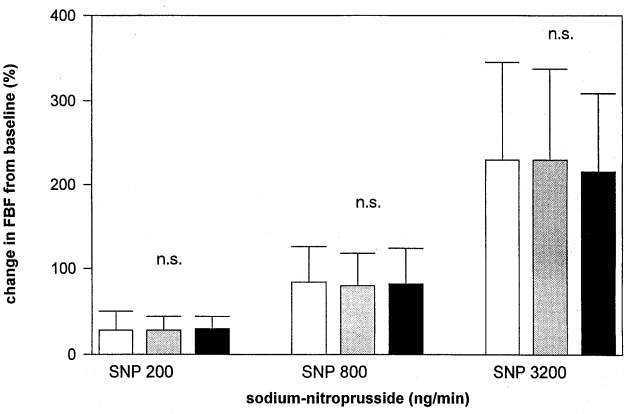
Figure 1. Percent change (mean ± SE) in forearm blood flow (FBF) during infusion of different doses of acetylcholine (ACH, μg/min) in subjects classified into tertiles by plasma Lp(a) levels. **Open bars** = lower tertile; **shaded bars** = middle tertile; **solid bars** = upper tertiles.

Endothelium-dependent vasodilation. Forearm blood flow before the administration of acetylcholine was 4.11 ± 1.44, 4.52 ± 1.26 and 4.20 ± 0.95 ml/min per 100 ml in the lower, middle and upper tertile, respectively (p = NS). A dose-dependent increase in blood flow was measured for acetylcholine in all tertiles ($p < 0.001$). No significant differences in forearm blood flow changes from baseline were noted among tertiles (Fig. 1).

Endothelium-independent vasodilation. Before administration of sodium nitroprusside, forearm blood flow was 5.20 ± 1.69, 5.89 ± 2.19 and 5.27 ± 1.72 ml/min per 100 ml in the lower, middle and upper tertile, respectively (p = NS). A similar dose-dependent increase in blood flow was measured for endothelium-independent vasodilation in all tertiles ($p < 0.001$). No significant differences in forearm blood flow changes from baseline were observed among tertiles (Fig. 2).

Basal production and release of nitric oxide (NO). Before the administration of L-NMMA, forearm blood flow was

Figure 2. Percent change (mean ± SE) in forearm blood flow (FBF) during infusion of different doses of sodium nitroprusside (SNP, ng/min) in subjects classified into tertiles by plasma lipoprotein(a) levels. **Open bars** = lower tertile; **shaded bars** = middle tertile; **solid bars** = upper tertile.



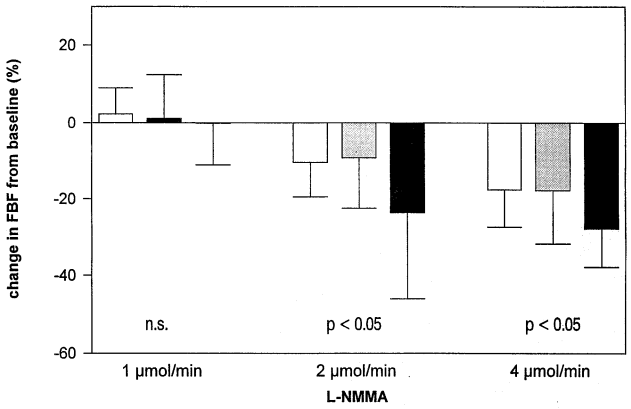


Figure 3. Percent change (mean ± SE) in forearm blood flow (FBF) during infusion of different doses of L-NMMA (µmol/min) in subjects classified into tertiles by plasma Lp(a) levels. **Open bars** = lower tertile; **shaded bars** = middle tertile; **solid bars** = upper tertile.

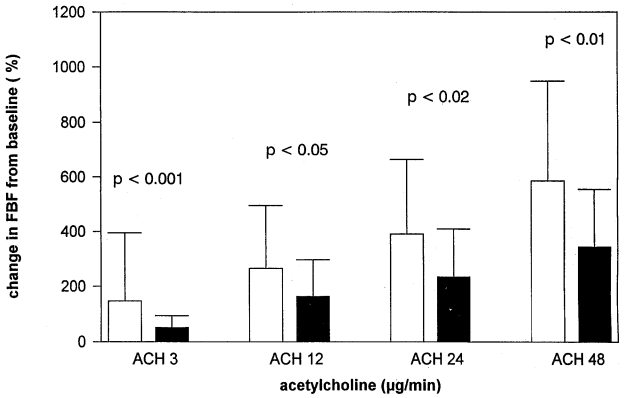


Figure 5. Percent change (mean ± SE) in forearm blood flow (FBF) during infusion of different doses of acetylcholine (ACH) in subjects with low **(open bars)** and high **(solid bars)** LDL cholesterol.

5.02 ± 1.32, 5.85 ± 2.08 and 5.81 ± 1.37 ml/min per 100 ml in the lower, middle and upper tertile, respectively (p = NS). Percent changes from baseline after the administration of different doses of L-NMMA are shown in Figure 3. L-NMMA caused a decrease in forearm blood flow in a dose-dependent manner in all tertiles ($p < 0.001$). However, changes in forearm blood flow in response to L-NMMA differed among tertiles (ANOVA, $p < 0.02$). Subsequent tests revealed significant differences among tertiles for 2 and 4 µmol/min of L-NMMA, with the greatest vasoconstriction occurring in the tertile with the highest Lp(a) concentration (each $p < 0.05$). These differences were significant even after total cholesterol, HDL cholesterol, triglycerides and LDL cholesterol were taken into account ($p < 0.05$). In accordance, Lp(a) concentrations correlated significantly with changes in forearm blood flow after the administration of 4 µmol/min of L-NMMA ($r = -0.38$, $p < 0.006$) (Fig. 4) and tended to be related to values after 2 µmol/min of L-NMMA ($r = -0.26$, $p = 0.06$) and 1 µmol/min of L-NMMA ($r = -0.26$, $p = 0.06$).

By multiple stepwise regression analysis, plasma Lp(a) level was the strongest determinant of forearm blood flow changes in response to L-NMMA (4 µmol/min of L-NMMA: $R^2 = 0.33$, beta = −0.44, $p < 0.01$). Total cholesterol, HDL cholesterol or LDL cholesterol did not emerge as independent determinants. Thus, Lp(a) appeared to be the most important determinant of basal production and release of NO in our study group.

Analysis for LDL cholesterol. In a subsequent analysis we tested the interaction between LDL cholesterol and forearm blood flow changes in response to acetylcholine by classifying subjects into groups with an LDL cholesterol concentration <160 or ≥160 mg/dl. Significant differences were observed between groups with low and high LDL cholesterol levels for all acetylcholine doses tested (3 µg/min, 146.9 ± 145.7% vs. 51.9 ± 42.4% [$p < 0.001$]; 12 µg/min, 265.9 ± 228.9% vs. 164.7 ± 133.9% [$p < 0.05$]; 24 µg/min, 391.1 ± 273.6%

Figure 4. Relation between Lp(a) concentration and changes in forearm blood flow (FBF) after infusion of L-NMMA (4 µmol/min) ($p < 0.02$ between groups and $p < 0.05$ for the upper tertile versus the middle and the lower tertile by ANOVA).

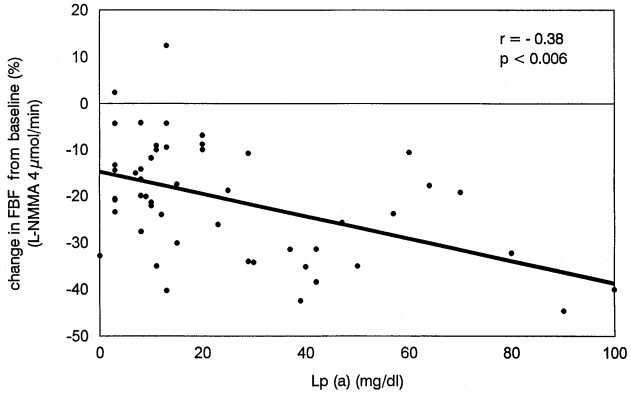
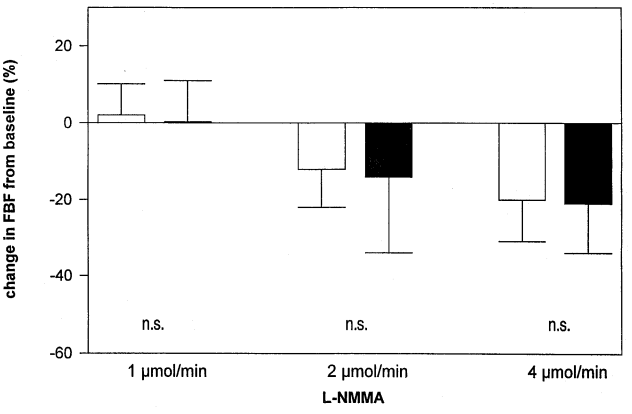


Figure 6. Percent change (mean ± SE) in forearm blood flow (FBF) during infusion of different doses of L-NMMA in subjects with low **(open bars)** and high **(solid bars)** LDL cholesterol.



vs. 234.7 ± 175.9% [p < 0.02]; 48 μg/min, 586.0 ± 363.3% vs. 344.8 ± 211.5% [p < 0.003]) (Fig. 5) but not for L-NMMA (1 μmol/min, 2.1 ± 8.2% vs. 0.26 ± 11.1% [p = NS]; 2 μmol/min, −12.7 ± 10.5% vs. −14.9 ± 20.8% [p = NS]; 4 μmol/min, −20.0 ± 11.0% vs. −21.7 ± 13.7% [p = NS]) (Fig. 6).

Discussion

An elevated Lp(a) plasma concentration has been identified (1–5,12) as an independent risk factor for coronary heart disease, stroke and peripheral atherosclerosis. In the current study we tested the hypothesis that the increased cardiovascular risk associated with elevated Lp(a) plasma levels might be mediated by an impairment of endothelial function. In our study, endothelium-dependent vasodilation as tested by the administration of different doses of acetylcholine was not impaired. Therefore, NO-mediated vasodilator response did not seem to be impaired by Lp(a) in our study cohort. Furthermore, endothelium-independent vasodilation as assessed by infusion of sodium nitroprusside was similar in the groups with low, medium and high Lp(a) concentrations. Therefore, the response to exogenous NO administration did not seem to be impaired by Lp(a) in our middle-aged subjects.

Our most intriguing finding is the significant difference observed in response to the inhibition of basal NO production and release by L-NMMA, with an increased vasoconstriction in subjects with relatively high levels of Lp(a). This difference remained significant even after other factors, known to influence endothelium-dependent vasodilation, such as total cholesterol, LDL and HDL cholesterol, were taken into account. By multiple stepwise regression analysis, plasma Lp(a) level emerged as the strongest determinant of vasoconstrictive response in the forearm vasculature to administration of L-NMMA.

Interpretation of vasoreactive response. Previous studies (25,26) have demonstrated that the highest dose of L-NMMA used in our study is at the top of the dose-response curve. These data suggest that we used a complete blockade of basal NO synthesis in our setting. Sudhir et al. (27), who found an increased vasoconstrictor response to L-NMMA in women taking supplementary estrogen interpreted these data as a hint for an increased basal NO synthesis, as estrogen has been found (28) to stimulate constitutive NO synthase in cell culture experiments. In addition, the response to L-NMMA was found (29) to be greater in young, healthy premenopausal women taking oral contraceptives than in those not taking them. Therefore, the increased vasoconstrictor response to the administration of L-NMMA observed in our subjects appears to reflect an increased basal NO production and release by high Lp(a) levels.

Cardiovascular risk factors and endothelial function. In early atherosclerosis, impaired endothelial function is the first indicator of vascular structural changes (6). Some cardiovascular risk factors such as arterial hypertension (6) and hypercholesterolemia (20,21) have been shown to impair stimulated endothelium-dependent vasodilation. This observation was confirmed in our study for the cardiovascular risk factor hypercholesterolemia, but not for elevated Lp(a). In subjects exposed to the cardiovascular risk factors of smoking (30) or diabetes mellitus (26), basal NO synthesis has been found to be impaired. Calver et al. (26) found a reduced response to blockade of NO synthesis with L-NMMA in the forearm vasculature in patients with insulin-dependent diabetes, indicating a diminished contribution of NO to overall forearm vascular tone. The observation of a similarly reduced response to sodium nitroprusside in the diabetic patients was interpreted as a reduced sensitivity of the vascular smooth muscle to NO. In our study, basal NO production and release were not impaired in subjects with the cardiovascular risk factor elevated Lp(a). In contrast, elevated Lp(a) levels were associated with increased basal NO production and release. Furthermore, the vasodilator response to sodium nitroprusside was not impaired by elevated Lp(a) concentrations in our study group. Therefore, in our study, neither a diminished sensitivity of the vascular smooth muscle to NO nor a decreased stimulated or basal NO synthesis as found for other cardiovascular risk factors appeared to account for Lp(a)-induced atherosclerotic effects.

Lp(a) and endothelial function. In a study by Tsurumi et al. (31), elevated Lp(a) levels were associated with impaired endothelium-dependent vasodilation in the coronary arteries. Sorensen et al. (32) found that flow-mediated dilation was inversely related to Lp(a) in the superficial femoral artery in hypercholesterolemic children. However, because basal production and release of NO were not assessed in these studies, it is not known whether basal NO synthesis was altered in those patients. Furthermore, there are important differences among the study cohorts in age, cardiovascular risk factor profile and the vascular bed under examination. Subjects in the study by Tsurumi et al. had a mean age of 58 ± 9 years compared with 37 ± 14 years in our patients, and increasing age is known to impair endothelial function. Whereas we included only subjects with no clinical evidence of atherosclerosis, the patients in the study by Tsurumi et al. had been referred for cardiac catheterizaton and suffered from chest pain. In addition, a large number of patients presented with cardiovascular risk factors such as smoking and hypertension. Sorensen et al. (32) found an inverse relation between Lp(a) and flow-mediated dilation only in children with hypercholesterolemia but not in control subjects. Whether this effect was due to elevated Lp(a) levels or to the coexisting hypercholesterolemia cannot be answered from these data. In our study subjects with high Lp(a) levels, we found an increased basal NO synthesis that was independent of total, HDL and LDL cholesterol. With respect to these important differences and the fact that basal synthesis of NO was not assessed in the studies of Tsurumi and Sorensen, the mechanisms underlying these conflicting results cannot be conclusively clarified.

Possible pathophysiologic mechanisms. The regulation of vascular tone is based on a balance between vasodilator and vasoconstrictive components. It is well established that NO is an important, although not the only, mediator of long-term

control of vasodilator tone (33). Because stimulated NO production and release were not impaired in our subjects with high Lp(a) levels, and basal NO synthesis was even increased, Lp(a)—in contrast to other cardiovascular risk factors—appears to exert its atherogenetic properties by mechanisms other than impairment of NO synthesis. An increased basal production and release of NO might represent a compensatory mechanism to counteract Lp(a)-induced atherosclerotic and vasoconstrictive effects, which are not yet understood. Physiologically released NO inhibitors might be increased by Lp(a) with the consequence of an enhanced NO synthesis to maintain vascular tone (33). Lp(a) might interact with intracellular NO storages, whose importance was shown by Davisson et al. (34) when they found progressively smaller vasodilator responses to successive injections of acetylcholine and bradykinin after NO synthase inhibition in rats. Alternatively, Lp(a) could be involved in the stimulation of local production of vasoconstrictors such as endothelin (35). To date, no data are available on the interaction between Lp(a) and NO storage capacities or other factors mentioned favoring one of these mechanisms to explain the Lp(a)-induced increase in basal NO synthesis. The increased contribution of NO to overall vascular tone as observed in our subjects with high Lp(a) might predispose these subjects to an increased vulnerability to other factors interfering with NO synthesis, such as smoking (17,30), diabetes mellitus (26), hypertension (6) or hypercholesterolemia (20,21).

Conclusions. In conclusion, our results argue against the hypothesis that Lp(a) acts on the endothelium through a well defined NO pathway in the manner described for LDL cholesterol, arterial hypertension, diabetes mellitus or smoking. Neither stimulated NO synthesis nor basal NO production and release seemed to be impaired by elevated Lp(a) concentrations. Our study was not designed to demonstrate the underlying pathogenetic mechanisms of why production and release of NO in patients with high Lp(a) are increased. However, identification of the pathophysiologic mechanisms underlying the increased basal NO synthesis in subjects with elevated Lp(a) might provide new insights into the regulatory process of endothelium-dependent vasorelaxation and should be pursued in further studies.

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