# Renovascular arteriovenous differences in Lp[a] plasma concentrations suggest removal of Lp[a] from the renal circulation

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**Abstract** High plasma concentrations of lipoprotein[a] (Lp[a]) are considered a genetically determined risk factor for atherosclerosis. Lp[a] is produced by the liver. The site(s) and mechanism(s) of catabolism are presently unclear. Lp[a] is elevated secondary to end-stage renal disease which suggests a direct or indirect role of the kidney in the metabolism of Lp[a]. We therefore investigated, by a simple in vivo approach, whether Lp[a] is removed by the human kidney. Lp[a] plasma concentrations were measured simultaneously by various methods in the ascending aorta and renal vein of 100 patients undergoing coronary angiography or coronary angioplasty. Lp[a] levels differed significantly between the two vessels even after correcting for hemoconcentration (20.1 ± 21.6 mg/dL versus 18.7 ± 20.3 mg/dL, $P < 0.001$). This corresponds to a mean arteriovenous difference of −1.4 mg/dL or −9% of the arterial concentration. No Lp[a] or intact apo[a] could be detected in urine from healthy probands. Although we cannot assign the kidney a regulatory role for Lp[a] plasma levels in humans with normal renal function, we conclude from our data that substantial amounts of this atherogenic lipoprotein are taken up by the kidney. The underlying mechanisms are unknown at the moment. This study therefore demonstrates for the first time that the human kidney plays an active role in the catabolism of Lp[a]. This may explain the elevated Lp[a] concentrations found in patients with chronic renal insufficiency.—**Kronenberg, F., E. Trenkwalder, A. Lingenhel, G. Friedrich, K. Lhotta, M. Schober, N. Moes, P. König, G. Utermann, and H. Dieplinger.** Renovascular arteriovenous differences in Lp[a] plasma concentrations suggest removal of Lp[a] from the renal circulation. *J. Lipid Res.* 1997. **38:** 1755–1763.

**Supplementary key words** Lp[a] catabolism • apolipoprotein[a] • arteriovenous • concentration difference • metabolism • kidney

Lipoprotein[a] (Lp[a]) differs in structure from low density lipoprotein (LDL) by the additional presence of the glycoprotein apolipoprotein[a] (apo[a]) which is covalently linked to the apolipoprotein B moiety of LDL (1). The extremely wide range of Lp[a] plasma concentrations (<0.1 to >300 mg/dL) among individuals of a population is controlled by variation at the apo[a] gene locus which is highly polymorphic in size due to a variable number of plasminogen-like kringle IV (K-IV) repeats (2, 3). Lp[a] is synthesized by the liver (4). Turnover studies in healthy humans indicated that Lp[a] levels are determined by the production rate (5, 6). Conflicting findings concerning the location and mechanism of catabolism have been reported (7, 8).

Numerous studies have described elevated plasma concentrations of Lp[a] in patients with end-stage renal disease (ESRD) (9) (for review see reference 10). Recently, we have demonstrated that the elevation of Lp[a] is not explained by differences in apo[a] isoform frequencies (11, 12). The elevated plasma Lp[a] concentrations in ESRD patients are, therefore, believed to be non-genetic and secondary to the disease. These observations suggest a role of the kidney in the metabolism of Lp[a], which may be either a direct catabolic function of the kidney or, alternatively, an indirect influence on the synthesis of Lp[a] in the liver or on the catabolism elsewhere.

The kidney has been assigned an extracting function for various lipoproteins and apolipoproteins in rat and rabbit models. High density lipoprotein and its protein constituents apolipoprotein A-I and apolipoprotein E

Abbreviations: Lp[a], lipoprotein[a]; apo[a], apolipoprotein[a]; LDL, low density lipoprotein; K-IV, kringle IV; LMW, low molecular weight; HMW, high molecular weight; ESRD, end-stage renal disease.

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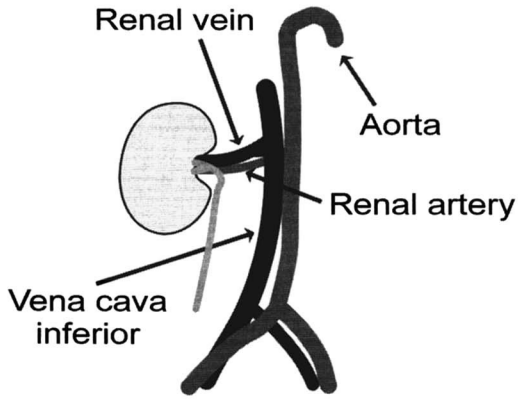


**Fig. 1.** Schematic illustration of the sites of blood withdrawal. Lp[a] was measured in EDTA-plasma collected from the ascending aortic segment and the renal vein of 100 patients. Additionally, it was measured in plasma from the vena cava below the aperture of the renal vein of five patients. After the withdrawal of venous blood the correct position of the catheter tip was verified by contrast injection.

have been shown to be degraded by the kidney after filtration and reabsorption of apolipoproteins in their free form (13, 14). The rat kidney also takes up apolipoprotein A-IV, although to a lesser extent than apolipoprotein A-I (15). In contrast, LDL is mostly taken up by the liver and adrenals (16).

The aim of our study was to investigate in vivo a possible extracting function of the human kidney for Lp[a]. We therefore measured the arteriovenous differences in Lp[a] plasma concentrations between the arterial and venous vascular system of the kidney, expecting lower plasma levels in the renal vein under the assumption of Lp[a] removal.

## METHODS

### Patients and procedure of blood sampling

A total of 100 patients (63 men and 37 women) undergoing coronary angiography (n = 53), percutaneous transluminal coronary angioplasty (n = 43), or percutaneous transseptal mitral commissurotomy (n = 4) were included in this study. They were on average 60.8 ± 10.3 years old, without renal insufficiency and showed an age-appropriate renal function (plasma creatinine 1.01 ± 0.22 mg/dL).

Patients were investigated following the Judkins' technique (17). Punctures of the right femoral artery and vein were performed. For the arterial vessel we used standard 8 French diagnostic coronary catheters (Cordis®). As there was no difference between the Lp[a] concentrations between plasma samples withdrawn from the ascending aorta and the renal artery (data not shown), arterial blood samples in this study were taken from the ascending aortic segment (**Fig. 1**). For the venous vessel we used 7 French thermodilution Swan Ganz catheters (Biosensors International®). After withdrawal of blood from the renal vein, this catheter was used for the measurement of pressure in the pulmonary circulation. Venous blood samples were taken from the renal vein and in five patients additionally from the vena cava below the aperture of the renal vein (Fig. 1). After the withdrawal of venous blood, the correct position of the catheter tip was verified by contrast injection. In order to rule out systemic concentration differences independent from the kidney, Lp[a] was also measured in the radial artery and the antecubital vein of five intensive care patients with a permanent catheter used for the intravasal determination of blood pressure in the arterial vessel.

Patients gave their written informed consent prior to investigation. In all patients the punctures for the arterial and venous catheters were already performed for diagnostic purposes, therefore posing no additional physiological or emotional load.

### Laboratory procedures

Lp[a], and IgM were measured from arterial and venous EDTA plasma samples that were frozen and kept at −80°C pending analysis (18). To minimize the variability of methodology, the arterial and venous samples from each patient were measured during the same assay run. Each sample was diluted and analyzed in quadruplicate. By this method the intraassay coefficient of variation was 1.78% for Lp[a] and 1.75% for IgM.

IgM was measured using the Behring nephelometric analyzer. In consideration of the expected hemoconcentration due to urinary output, the venous plasma levels of Lp[a] were corrected for the individual IgM plasma concentration changes between arterial and venous blood with the formula:

$$\text{Lp[a]venous (corrected)} = \frac{\text{IgMarterial}}{\text{IgMvenous}} \times \text{Lp[a]venous}$$

For further calculations only the corrected venous plasma levels were used.

Lp[a] quantification was performed with a double-antibody ELISA using an affinity-purified polyclonal rabbit anti-apo[a] antibody for coating and the horseradish peroxidase-conjugated monoclonal antibody 1A2 for detection (1A2-ELISA) (18). This antibody does not crossreact with plasminogen and recognizes an epitope of the repetitive K-IV motif of apo[a] (19). Lp[a] measurement was repeated by three additional methods in a subset of 20 patients selected for their marked arteriovenous Lp[a] differences and with Lp[a] plasma concentrations ranging from 2 mg/dL to 80 mg/dL. One of these methods was an ELISA using an

affinity-purified polyclonal rabbit anti-apo[a] antibody for coating and the monoclonal antibody 5A5 for detection (5A5-ELISA). This antibody neither crossreacts with plasminogen nor with catalase and therefore recognizes a different epitope (H. Dieplinger and G. Utermann, unpublished results). The other two assays were performed by DELFIA (20) in an external laboratory blinded for the site of blood withdrawal. One assay quantifies Lp[a] by an affinity purified antibody against apo[a] for both capture and detection ([a]–[a] DELFIA). The other assay used an affinity-purified polyclonal antibody against human apoB-100 for detection ([a]–B DELFIA) (20).

We estimated in both vessels the amount of free apo[a] that is not bound to apoB-100 in an Lp[a] complex and that consists mostly of apo[a] degradation products (21) by the following procedure. Fifty µl of plasma was incubated with 100 µl of apoB-antiserum for 16 h at 4°C. After centrifugation for 10 min in an Eppendorf high-speed centrifuge, apo[a] was measured in the supernatant by the same ELISA procedure described above, yielding the amount of free apo[a]. To exclude insufficient Lp[a] precipitation, apoB was also monitored in parallel in the same supernatants with an ELISA previously described (18). In addition, supernatants were analyzed by immunoblotting with the antibodies 1A2 and 5A5.

Apo[a] immunoreactivity was also measured in urine by 1A2-ELISA. The presence of apo[a] was additionally investigated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE), followed by immunoblotting of 50 times concentrated urine using the Centricon microconcentrator (Amicon®, Beverly, MA). The lower detection limit in immunoblots was 1 ng apo[a].

Apo[a] phenotyping of plasma samples was performed by SDS agarose gel electrophoresis under reducing conditions as outlined (22) with the modification of applying 50 ng of Lp[a] onto the gel. Immunoblotting was done with the monoclonal anti-apo[a] antibody 1A2 (23). In three subjects with low Lp[a] plasma concentrations no apo[a] isoforms were detectable.

In a random subgroup of 20 patients, we measured the arteriovenous differences of plasma creatinine by a commercially available enzymatic assay using creatinine amidohydrolase and triarylimidazol (Boehringer Mannheim, Germany).

### Statistical analysis

Differences in measured parameters between the arterial and venous plasma samples were assessed by the paired Wilcoxon test (Lp[a] and IgM) or by the paired *t*-test (creatinine). For Lp[a] the arteriovenous differences were calculated separately for three apo[a] phenotype groups according to the molecular weight (defined by the number of K-IV repeats) of the smaller apo[a] band (24, 25). ΔLp[a] of these three groups was compared by ANOVA analysis with Bonferroni correction for multiple comparisons. The Spearman rank correlation coefficients were calculated between the variables ΔLp[a], $Lp[a]_{art}$, and the number of K-IV repeats of the smaller apo[a] allele. Stepwise multivariate regression analysis was applied to investigate the influence of different parameters on ΔLp[a]. For the forward variable selection process, $P < 0.10$ was chosen.

Statistical analysis was performed with SPSS for Windows, Release 6.1.3. (Chicago, IL). A $P < 0.05$ was considered significant.

## RESULTS

We observed a significant difference for Lp[a] in plasma samples collected simultaneously from the ascending aorta and the renal vein with lower levels in the vein: 20.1 ± 21.6 versus 19.0 ± 20.8 mg/dL for Lp[a] ($P < 0.001$). IgM was measured in the same plasma samples and showed an arteriovenous increase from 142.7 ± 89.8 mg/dL to 143.5 ± 90.0 mg/dL ($P < 0.05$) with a mean change of 0.9%. The venous plasma levels of Lp[a] were corrected for the individual IgM concentration changes to correct for hemoconcentration by the kidney due to urinary output (for the formula see Methods). After this correction the mean Lp[a] concentration in the venous sample was 18.7 ± 20.3 mg/dL ($P < 0.001$) corresponding to a mean arteriovenous difference (ΔLp[a]) of −1.4 mg/dL or −9% of the arterial concentration (**Table 1**). Subjects with low molecular weight (LMW) apo[a] isoforms (11–22 K-IV repeats) had a significantly higher ΔLp[a] than those from groups with high molecular weight (HMW) isoforms (23–25 and 26–40 K-IV repeats): −2.8 mg/dL versus −1.4 and −1.1 mg/dL, respectively, $P < 0.01$ (Table 1 and **Fig. 2**). Patients from the group with the largest apo[a] isoforms (26–40 K-IV repeats) showed the highest relative arteriovenous difference (−10.9% versus −6.8% and −6.4%).

ΔLp[a] correlated with $Lp[a]_{art}$ ($r = -0.70$, $P < 0.001$) (**Fig. 3**) and the number of K-IV repeats of the smaller apo[a] isoform ($r = 0.20$, $P < 0.05$). Multivariate regression analysis revealed that $Lp[a]_{art}$ explains most of the arteriovenous difference (**Table 2**). The number of K-IV repeats of the smaller apo[a] allele failed to be significant presumably due to the close correlation with Lp[a] concentrations.

To exclude an error of analysis by our assay system, we repeated the measurement of Lp[a] in a subset of 20 selected patients by three different assays using dif-

TABLE 1. Arterial and venous plasma concentrations and absolute and relative concentration changes of Lp[a] between the two vessels

| Apo[a] Phenotype Group | n | Concentration | | Δ Concentration | | |
|---|---|---|---|---|---|---|
| | | Arterial | Venous | mg/dL | % | $P<$ |
| 11–22 K-IV repeats | 17 | 45.1 ± 23.6 | 42.3 ± 22.1 | −2.8 ± 2.2 | −6.8 | 0.001 |
| 23–25 K-IV repeats | 23 | 21.0 ± 22.3 | 19.7 ± 21.0 | −1.4 ± 1.7 | −6.4 | 0.001 |
| 26–40 K-IV repeats | 57 | 13.1 ± 14.5 | 12.0 ± 13.5 | −1.1 ± 1.6 | −10.9 | 0.001 |
| All apo[a] phenotypes | | 20.1 ± 21.6 | 18.7 ± 20.3 | −1.4 ± 1.8 | −9.0 | 0.001 |

Data are given separately for three apo[a] phenotype groups defined by the number of K-IV repeats of the smaller apo[a] isoform.

ferent antibodies directed against apo[a]. Two of these assays were performed in an external laboratory blinded for the site of blood withdrawal. All three methods observed a similar absolute and relative arteriovenous Lp[a] difference as our commonly used assay (**Table 3**).

We validated our experimental design as follows. Lp[a] was additionally measured in the vena cava below the aperture of the renal vein of five patients (Fig. 1). We detected no significant difference between the aorta and the vena cava but recorded lower values in the renal vein (32.4 versus 33.0 versus 31.0 mg/dL). This supports the Lp[a]-extracting function of the kidney. Lp[a] was also determined in the radial artery and the antecubital vein of five intensive care patients. This represents a further arteriovenous system study aimed to investigate whether the differences are caused by different conditions in the arterial and venous vessels. No significant difference for Lp[a] was observed between these two vessels (25.9 versus 26.3 mg/dL, n.s.). Finally, plasma creatinine, a substance for which the rate of elimination by the kidney is known, showed a decrease from 0.99 ± 0.17 mg/dL in the aortic sample to 0.84 ± 0.20 mg/dL in the renal vein ($P < 0.001$). This is equivalent to a mean decrease of 15.5%.

We measured, in a subset of 20 patients, the amount of free apo[a] immunoreactivity in plasma of the aorta and renal vein to investigate whether the apo[a] degradation products circulating in plasma (21) are elimi-

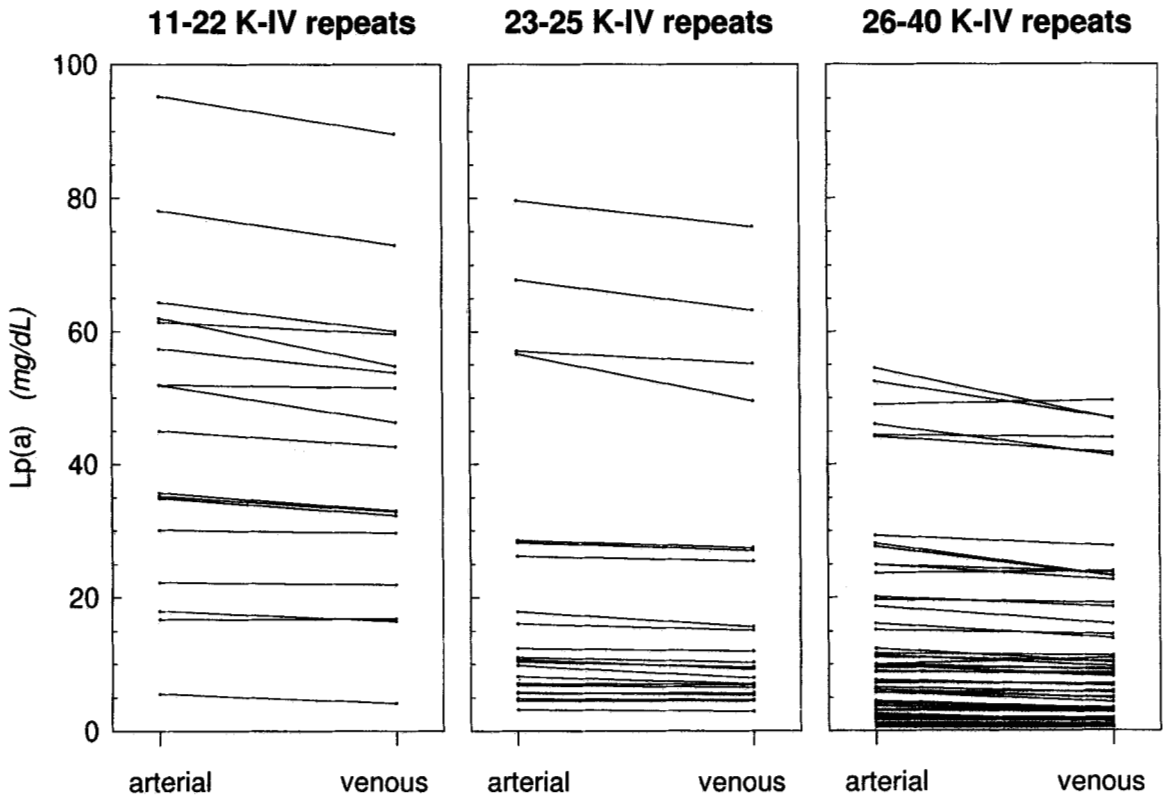


**Fig. 2.** Individual changes of Lp[a] plasma concentrations between the aorta and the renal vein in the three apo[a] isoform subgroups.

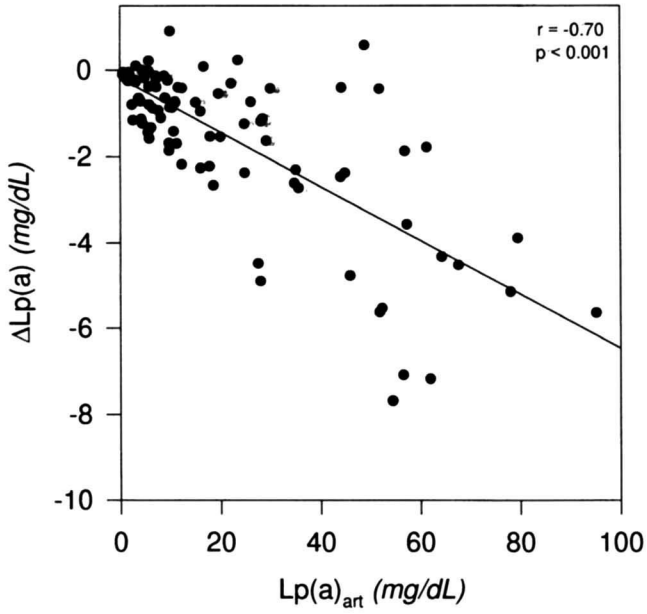


**Fig. 3.** Correlation between the Lp[a] plasma concentration (measured in the aorta) and the arteriovenous difference (ΔLp[a]).

TABLE 2. Results of stepwise regression analysis of the influence of Lp[a], the number of K-IV repeats of the smaller apo[a] allele, age, and sex on the absolute arteriovenous differences of Lp[a]

| Variable | Coefficient | S.E. | *P* | $R^{2a}$ |
|---|---|---|---|---|
| Constant | −0.1921 | 0.1836 | | |
| $Lp[a]_{art}$ | −0.0627 | 0.0060 | <0.0001 | 0.55 |
| Variables not in equation | | | | |
| Number of K-IV repeats of apo[a] allele | | | = 0.12 | |
| Age | | | = 0.87 | |
| Sex | | | = 0.96 | |

[a] $R^2$ of the stepwise procedure.

TABLE 3. Mean (±SD) arterial Lp[a] plasma concentrations and absolute and relative concentration changes of Lp[a] measured by four different assays in 20 selected plasma samples

| Assay | $Lp[a]_{art}$ | ΔLp[a] | ΔLp[a] |
|---|---|---|---|
| | *mg/dL* | | % |
| 1A2-ELISA | 28.8 ± 25.1 | −3.7 ± 3.2 | −19.1 ± 11.9 |
| 5A5-ELISA | 28.8 ± 23.7 | −3.9 ± 3.4 | −17.8 ± 10.9 |
| [a]–[a] DELFIA | 29.6 ± 26.3 | −4.2 ± 3.5 | −19.0 ± 11.6 |
| [a]–B DELFIA | 31.1 ± 33.7 | −4.0 ± 3.6 | −18.7 ± 12.9 |

1A2-ELISA: uses an affinity-purified polyclonal rabbit anti-apo[a] antibody for coating and the horseradish peroxidase-conjugated monoclonal antibody 1A2 for detection. 5A5-ELISA: uses the affinity-purified polyclonal rabbit anti-apo[a] antibody for coating and the monoclonal antibody 5A5 for detection. [a]–[a] DELFIA: uses an affinity-purified antibody against apo[a] for both capture and detection. [a]–B DELFIA: uses an affinity-purified polyclonal antibody against human apoB-100 for detection.

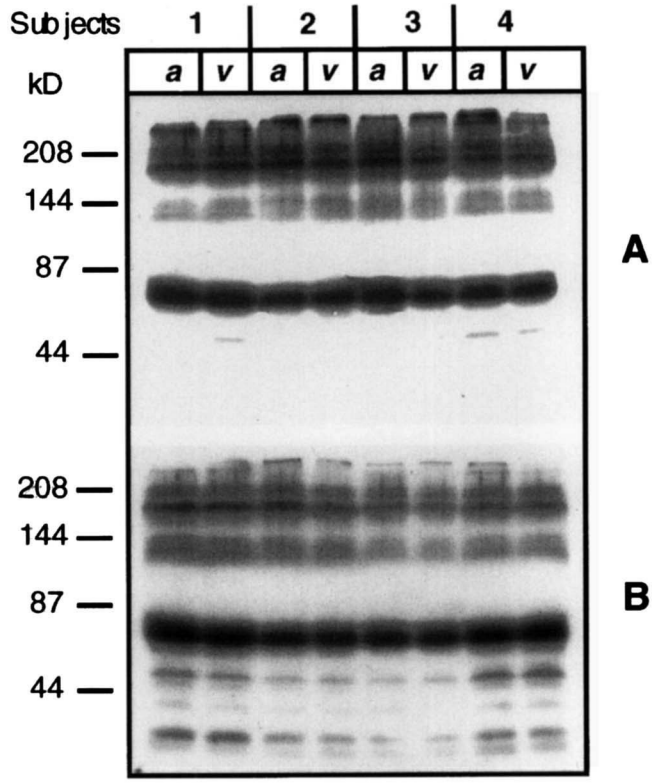


**Fig. 4.** Immunoblot analysis of free, non-LDL-bound apo[a] in plasma collected simultaneously from the aorta (*a*) and the renal vein (*v*) of four different subjects. Samples were applied under reducing conditions on a 10% SDS-polyacrylamide gel. Detection with the monoclonal antibodies 1A2 (A) and 5A5 (B). Bands with the highest molecular weight represent intact apo[a] whereas smaller bands correspond to apo[a] fragments. The pattern of apo[a] immunoreactivity was not different between the plasma of the two vessels.

nated by the kidney. We observed no significant arteriovenous differences analyzed quantitatively by ELISA (0.52 vs. 0.53 mg/dL, n.s.) or qualitatively as shown by immunoblotting after SDS-PAGE; the pattern of apo[a] immunoreactivity was not different between the plasma of the two vessels (**Fig. 4**).

A negligible apo[a] immunoreactivity was measured in urine by ELISA (0.025 ± 0.28 mg/dL). As in previous studies (21, 26–28), immunoblot analysis revealed no intact apo[a]. Instead, several bands smaller than the apo[a] isoforms of the corresponding plasma sample were detected by several antibodies against apo[a] (data not shown).

## DISCUSSION

Numerous studies have reported elevated plasma levels of Lp[a] in patients with ESRD, suggesting that the

kidney is involved in the metabolism of Lp[a] (9–12). To test whether the kidney plays a direct role in the metabolism of Lp[a], we measured the Lp[a] plasma concentrations in the arterial plasma from the ascending aorta and in the venous plasma from the renal vein. If the kidney was not a catabolic site for Lp[a], we would expect unchanged values or increased Lp[a] due to a hemoconcentrating effect of the kidney by urine excretion. On the other hand, a decrease in Lp[a] concentrations would signal an Lp[a] extracting function of the kidney for Lp[a]. We observed a highly significant decrease of Lp[a] from the arterial to the venous plasma from 20.1 ± 21.6 to 18.7 ± 20.3 mg/dL ($P < 0.001$). The extent of this decrease was mostly dependent on the arterial Lp[a] plasma concentration. This represents the first in vivo report of arteriovenous differences indicating a substantial renal function for removal of Lp[a] in humans.

### Arguments that the measured differences are not an artifact

The large difference between the arterial and venous plasma is unlikely to be the result of an error in analysis. In anticipation of small variation occurring in measurement, we sought to minimize technical errors by diluting and analyzing each sample in quadruplicate and including both plasma samples in the same assay run. By this procedure, the intraassay CV was 1.78% for Lp[a] and therefore does not explain the large arteriovenous differences of about 9%. In experiments with only few samples such as the measurement of Lp[a] in the other arteriovenous systems, we analyzed the samples up to 16 times.

An influence of the slightly different pH levels between the arterial and venous blood samples on the assay systems can be excluded as the plasma samples were buffered with 0.1% casein (pH = 7.3) by a sample dilution of 1:50 to 1:4000 for Lp[a]. Furthermore, we excluded an assay artifact by measuring Lp[a] by four different assays, two of them in a blinded experimental design in an external laboratory. We observed a similar absolute and relative arteriovenous Lp[a] difference by all four methods using different antibodies that recognize different epitopes (Table 3). Even the [a]-B DELFIA which measures apoB-100 of Lp[a] revealed highly correlative results. These control experiments convinced us that our findings reflect "real" concentration differences and were not the result of artifacts such as different epitope recognition by our antibodies in the arterial and venous samples. Finally, we excluded a different adsorption of Lp[a] or apoB by the arterial and venous catheters (data not shown).

Four lines of reasoning support the validity of this study. *1*) IgM concentration increased on average 0.9% from the arterial to the venous sample which is close to the value expected due to hemoconcentration. *2*) In a subgroup of 20 patients we measured creatinine in the arterial and venous plasma samples. Creatinine is an endogenous substance filtered freely in the glomeruli and not reabsorbed in the tubular system. The arteriovenous difference for creatinine was 15.5% which is in the range of the expected glomerular filtration fraction in patients of a mean age of 60 years. From the IgM and creatinine data we believe that the experimental protocol presented is appropriate for studying a possible contribution of the kidneys to Lp[a] removal. In other studies a similar approach was used to investigate the uptake of free fatty acids by the kidney in humans (29, 30). The authors described a net uptake between 5 and 10% of plasma free fatty acids which then provide the major metabolic fuel for the kidney. These results clearly demonstrate that this organ can extract large amounts of substrate by mechanisms distinct from filtration. *3*) We observed no significant ΔLp[a] between the aorta and the vena cava below the aperture of the renal vein, but significantly lower values in the renal vein. This supports the Lp[a]-extracting function of the kidney. *4*) We used the measurement of Lp[a] in the radial artery and an antecubital vein in five intensive care patients to demonstrate that the arteriovenous differences found in the renovascular bed are not simply caused by different conditions in the arterial and venous vessels. As the concentration differences could not be observed in other non-renovascular arteriovenous systems, we could exclude that these differences were artefactually caused by different blood pressure, flow velocity, or resistance, which could itself have a different influence on the distribution of Lp[a] in the blood stream.

### Limitations of the study

We cannot exactly calculate the clearance of Lp[a] as this requires the knowledge of the renal plasma flow in addition to the arteriovenous difference. As we have investigated 100 renally healthy subjects, we can only calculate an approximate value by anticipating a renal plasma flow of about 400–600 ml/min. This value, however, should be considered with caution, as the renal plasma flow is not constant over 24 h (31). The daily Lp[a] extraction rate calculated from this approximate value is about 8.4–12.5 g which is in strong contrast to the results of previous turnover studies. All these turnover studies were, however, performed with radioisotope-labeled purified Lp[a]. Highly purified Lp[a] has to be considered rather unstable and is reinjected to the circulation after radiolabeling. It is unclear whether this purified Lp[a] has the same physiological charac-

teristics as natural Lp[a]. Only studies using stable isotope techniques will finally clarify the true in vivo turnover of Lp[a].

One theoretical possibility that could explain the large arteriovenous differences is an extraction of Lp[a] from the renovascular circulation and a bypass transport through the lymphatic system to the systemic circulation. This would mean that the kidney simply removes Lp[a] but does not catabolize it. As it is extremely difficult to get samples of pure human lymph drawn from the ductus thoracicus, it will be hard to test this hypothesis.

**Possible involved mechanisms**

Any glomerular filtration of Lp[a] or even apo[a] is very unlikely due to the large size of the particles. Recent studies demonstrated apo[a] immunoreactivity in urine that was found to consist of apo[a] fragments (21, 26–28). Similar to the arteriovenous differences of Lp[a], the amount of urinary apo[a] correlated with the Lp[a] plasma concentrations. The size of the fragments ranged from 30 to 215 kDa. At least the larger peptides are therefore transported to urine by an unknown mechanism. Mooser et al. (27) observed that the intravenous administration of purified urinary apo[a] fragments into mice resulted in a rapid appearance of the same fragments in urine, which suggests that this transport is very fast. From these findings the authors concluded that apo[a] fragments found in urine might be formed extrarenally and then excreted by the kidney. They furthermore described apo[a] fragments in plasma ranging in size from about 125 to 360 kDa (21). When these purified plasma fragments were injected intravenously into mice, most of the fragments were cleared from the plasma after 5 h and appeared in urine. Urinary fragments were smaller in size than those injected. In our study we therefore analyzed free apo[a] immunoreactivity quantitatively as well as qualitatively between the renal artery and vein. There was no quantitative (0.52 vs. 0.53 mg/dL, n.s.) or qualitative difference (Fig. 4) between the two vessels, which at a first glance may suggest that the kidney does not clear these fragments. An alternative interpretation is that the kidney might be the site of clearance as well as of production of these fragments. This would also result in a similar quantitative and qualitative pattern of apo[a] immunoreactivity in the two vessels.

The apo[a] immunoreactivity measured in urine was about $0.025 \pm 0.028$ mg/dL which is similar as reported by others (21, 26–28). Kostner et al. (28) calculated that less than 1% of the Lp[a] catabolism is explained by excretion of apo[a] fragments in urine. This calculation, however, assumes that the apo[a] fragments are quantified in the same way as the intact apo[a] particle. Because most of the antibodies used for the quantification of apo[a] are likely to recognize repetitive epitopes, it is possible that the assays either overestimate the amount of apo[a] in urine by recognizing several fragments from one apo[a] particle or that the assay underestimates apo[a] due to degradation of epitopes on the fragments. We therefore believe that a calculation of the relative amount of apo[a] excreted by the kidney from ELISA data may be very inaccurate or misleading.

Different cell types of the kidney have been described to express receptors thought to be involved in the catabolism of Lp[a]. The kidney has a very high blood flow and provides an imposing endothelial surface within its dense capillary network. Due to the high homology between apo[a] and plasminogen, a high density of plasminogen receptors might be available for apo[a] (32). Recent in vitro studies demonstrated an uptake of recombinant apo[a] in lipoprotein-unbound form especially by plasminogen receptors of fibroblasts and HepG2 cells, and an uptake of recombinant apo[a] complexed with LDL by the LDL receptor (33). Mesangial cells and glomerular endothelial cells express LDL receptors (34, 35). Recently, binding and uptake of Lp[a] could be demonstrated by these cell lines in culture, although with a lower affinity and specificity compared to LDL. However, binding of Lp[a] to extracellular mesangial matrix was enhanced compared to LDL (35). Immunohistochemical studies in rats revealed a marked expression of LDL receptor-related protein (LRP) on the surface of mesangial cells and hepatocytes (36). Whether these receptors are of major importance in vivo or whether other mechanisms are involved in the catabolism of Lp[a] is unknown at the moment.

Although we cannot assign the kidney a regulatory role for Lp[a] plasma levels in humans with normal renal function, we conclude from our data that substantial amounts of this atherogenic lipoprotein are removed by the kidney. This study therefore demonstrates for the first time that the human kidney plays an active role in the catabolism of Lp[a].

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