Contribution of Fibrinogen and Lipoproteins to Plasma Viscosity in Hypercholesterolemia and Hypertriglyceridemia: Evaluation by Selective Depletion of Low-Density Lipoproteins or Fibrinogen

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Epidemiological studies suggest that the plasma fibrinogen concentration is the main determinant of plasma viscosity (PV), but the concentration of other macromolecules (eg, immunoglobulins) and low-density lipoprotein (LDL) cholesterol and triglycerides are also correlated with PV. However, only a few data exist concerning the in vitro effects of these plasma constituents on PV. Therefore, we investigated PV before and after the specific elimination of fibrinogen and LDL in hypercholesterolemic and hypertriglyceridemic plasma. First, hypercholesterolemic samples (n = 7) were pumped simultaneously through 2 columns: a fibrinogen-depleting column containing the pentapeptide Gly-Pro-Arg-Pro-Lys (GPRPK) and a LDL-depleting column containing specific antibodies against apolipoprotein B-100. In the plasma and in each fraction from the column, the cholesterol level was measured enzymatically, fibrinogen was determined by immunonephelometry, and PV was analyzed using a low-shear rotation viscosimeter. After the fibrinogen-depleting column, the fibrinogen concentration decreased from 3.21 ± 0.20 to 0.94 ± 0.16 g/L ($P < .005$), inducing a decrease in PV from 1.27 ± 0.02 to 1.17 ± 0.01 mPas (milliPascal seconds) ($P < .005$). Despite a marked reduction of the LDL cholesterol after the LDL-depleting column (from 6.40 ± 0.23 to 4.08 ± 0.32 mmol/L, $P < .005$), PV remained unchanged. Second, hypertriglyceridemic samples (n = 7) were pumped through the fibrinogen-depleting column, which reduced the fibrinogen concentration from 4.29 ± 0.79 to 1.62 ± 0.69 g/L ($P < .001$) and PV from 1.42 ± 0.06 to 1.03 ± 0.05 mPas ($P < .01$) while the triglyceride concentration remained unchanged. Our results confirm the epidemiological correlation between the fibrinogen concentration and PV in patients with hypercholesterolemia and hypertriglyceridemia. The influence of fibrinogen on PV seems much more pronounced than the direct effect of lipoprotein concentrations. Therefore, the elevated PV in patients with hypercholesterolemia and especially with hypertriglyceridemia seems mainly due to elevated fibrinogen levels.

PATIENTS WITH HYPERCHOLESTEROLEMIA have an elevated risk for cardiovascular disease.[1] The mechanisms by which atherosclerosis is triggered in these patients are not completely understood. However, atherosclerosis seems at least partly mediated by hemorrheological factors, eg, an elevated fibrinogen concentration and high plasma viscosity (PV). Patients with hypercholesterolemia are known to have higher PV than healthy subjects,[2] but it is not known why PV is elevated in these patients. Since low-density lipoprotein (LDL) cholesterol has also been found to be correlated with the fibrinogen concentration,[3-5] which is regarded as an important determinant of PV,[6] it is difficult to distinguish between the direct effect of LDL cholesterol on PV and the effect mediated by fibrinogen.

The knowledge that fibrinogen is a main contributor to PV is based on epidemiological studies in which PV correlated well with fibrinogen levels.[7] Only a few published investigations have evaluated the contribution of fibrinogen to PV in vitro. One of these experiments was a comparison between the viscosity of serum (in which fibrinogen is eliminated) and plasma that showed a higher viscosity for plasma.[8] However, no conclusions concerning the association between different fibrinogen concentrations and PV can be derived from these data.

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To evaluate the contribution of different plasma constituents to PV in hypercholesterolemic samples, we selectively removed LDLs [including lipoprotein(a)] or fibrinogen from plasma in vitro by affinity chromatography.

PV has been shown to be higher in patients with hypertriglyceridemia[9] and chylomicronemia.[10] But it is still a matter of discussion as to why PV is high in these subjects. PV could be elevated because of a direct triglyceride effect or because of secondary phenomena (eg, concomitantly elevated fibrinogen). The elucidation of the origin of elevated PV in severe hypertriglyceridemia may contribute to the knowledge of the pathogenesis of typical complications of chylomicronemia, especially acute pancreatitis. To investigate the influence of the fibrinogen concentration on PV in hypertriglyceridemic patients, we specifically eliminated fibrinogen from hypertriglyceridemic plasma with elevated PV.

The reason we investigated the effect of the fibrinogen and lipoprotein concentration on PV rather than blood viscosity is that the influence of plasma constituents is more pronounced on PV versus blood viscosity, because the possible effects of blood cells are eliminated. In addition, PV is a better-established atherosclerotic risk marker than whole-blood viscosity, probably due to the easier storage and measurement of viscosity in plasma samples. Moreover, complications from hypertriglyceridemia, especially acute pancreatitis, are thought to be the result of microcirculatory disturbances. In small vessels, PV is regarded as a better parameter for describing fluid flow than blood viscosity.

SUBJECTS AND METHODS

Subjects and Blood Collection

Twenty-one patients with mild hypercholesterolemia (total cholesterol between 5.20 and 7.40 mmol/L) and 7 patients with hypertriglyceridemia (total triglycerides between 3.75 and 48.14 mmol/L) participated

in the study after provision of informed consent. After an overnight fast, venous blood samples (60 mL in patients with hypercholesterolemia and 80 mL in patients with hypertriglyceridemia) were collected from an antecubital vein into EDTA tubes (2.0 mg K_3EDTA/mL blood; Greiner, Frickenhausen, Germany), plasma was obtained by centrifugation of EDTA blood (1,750 × *g* at 4°C for 20 minutes), and measurements were performed within 4 hours after blood collection.

Fibrinogen-Depleting Column

Peptides beginning with the *N*-terminal sequence Gly-Pro-Arg-Pro have been shown to bind fibrinogen and prevent polymerization of fibrin monomers.[11] Thus, the pentapeptide Gly-Pro-Arg-Pro-Lys (GPRPK) was synthesized as trifluoracetate by Saxon Biochemicals (Hannover, Germany). The peptide was shown to be pure (>97%) by high-performance liquid chromatography and then was coupled to Sepharose 4B gel as described by Kuyas et al.[12] In brief, 10 g Sepharose 4B gel was added to a 40-mmol/L solution of GPRPK-trifluoracetate, and the coupling occurred at room temperature on a rotatory plate. Afterward, the gel was washed with carbonate buffer, H_2O, isopropanol, and methanol, and 3 g GPRPK-Sepharose was placed in a column (1.2 × 6 cm). Fibrinogen binding specificity was proven by an experiment where the lyophilysates of the eluates (eluted with 0.2 mol/L glycine buffer, adjusted to pH 2.8 with HCl) after loading the column with fibrinogen (3 mg/mL) or plasma had the same band on sodium dodecyl sulfate gel electrophoresis.

LDL-Depleting Column

A column (1.2 × 6 cm) containing polyclonal apolipoprotein B-100 sheep antibodies coupled to cyanogen bromide–activated Sepharose 4B gel (Baxter, Unterschleißheim, Germany) was used for LDL removal.[13] To evaluate the specificity and efficacy of the column, 6 plasma samples were pumped through the column. The lipoprotein concentration in these samples and the corresponding first fractions after the column are shown in Table 1. This column also removes lipoprotein(a) and intermediate-density lipoproteins. Therefore, for the experiments on rheology, plasma samples with lipoprotein(a) less than 10 mg/dL were used to exclude the effects of lipoprotein(a) elimination on PV.

Study Design

The investigation, which was performed at 25°C, was divided into 2 experiments, one with hypercholesterolemic plasma samples and one with hypertriglyceridemic plasma samples. To evaluate the influence of fibrinogen and lipoprotein concentrations on PV in hypercholesterolemia, plasma samples from patients with mild hypercholesterolemia were analyzed simultaneously with 2 columns (fibrinogen-depleting column and apolipoprotein B-100–depleting column). Because of the large plasma requirement (90 mL), plasma samples (n = 7) were pooled from 3 mildly hypercholesterolemic samples each. Before starting the experiment, the 2 columns were each rinsed with 20 mL sodium chloride solution (9 g/L). A pooled plasma sample (2,000 IE Heparin; Braun, Melsungen, Germany; added to 80 mL plasma) was then pumped simultaneously through the 2 columns (plasma flow, 0.34 mL/min) using a parallel-tube pump (Minipuls 2; Gilson, Villiers de Bel, France). Because of the initial dilution effect of plasma, the column was preloaded with 3 mL plasma before the collection of filtered plasma was started in fractions at 3-minute intervals. After collection of the sixth fraction, 50 mL 0.2-mol/L glycine buffer (adjusted to pH 2.8 with HCl) was passed through the columns instead of the plasma sample in order to regenerate the columns, followed by a washing cycle with 50 mL phosphate-buffered saline containing 0.1 g/L sodium azide. Between experiments, the columns were stored at 4°C. Before the next use, they were rinsed with sodium chloride (9 g/L) again. We used the fibrinogen-depleting column 25 times and the LDL-depleting column 15 times (evaluation and experiment) without a decline in efficacy.

To evaluate the contribution of the fibrinogen concentration to PV in hypertriglyceridemic patients, plasma samples from 7 hypertriglyceridemic patients were investigated with the fibrinogen-depleting column. Because only 1 column was used in this experiment, each plasma sample (1,000 IE Heparin; Braun; added to 40 mL plasma) was derived from only 1 single patient. The experiment was performed as already described.

Table 1. Lipoprotein Concentrations Before and After Apolipoprotein B-100–Depleting Column (n = 6)

Variable	Before Column	After Column
Total cholesterol	7.85 ± 0.57	4.24 ± 0.43†
Total triglycerides	1.35 ± 0.12	1.03 ± 0.10†
HDL cholesterol	1.38 ± 0.18	1.39 ± 0.19
IDL cholesterol	0.41 ± 0.06	0.22 ± 0.05*
LDL cholesterol	5.84 ± 0.59	2.49 ± 0.42†
VLDL cholesterol	0.61 ± 0.09	0.49 ± 0.07*
VLDL triglycerides	1.10 ± 0.18	0.91 ± 0.14*
Lipoprotein(a)	19.2 ± 7.8	5.2 ± 1.9*

NOTE. All values are the mean ± SEM in mmol/L except lipoprotein(a), which is mg/dL.

Abbreviations: HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; VLDL, very-low-density lipoprotein.

*$P < .05$.

†$P < .005$.

Lipoprotein and Hemorrheological Measurements

Triglyceride and cholesterol levels in plasma and in filtered fractions were measured enzymatically using reagents from Boehringer (Mannheim, Germany). The cholesterol level was measured using the enzymes cholesterol esterase, cholesterol oxidase, and peroxidase, and triglyceride measurement was performed using the enzymes lipase, glycerol kinase, glycerol-3-phosphate oxidase, and peroxidase. The resulting colored product was quantified photometrically by an autoanalyzer (EPOS Autoanalyzer; Eppendorf, Hamburg, Germany). PV was measured at 37°C with a Contraves 30 low-shear rotation viscosimeter (Contraves, Zurich, Switzerland) at a shear rate of 115/s. Temperature was kept constant at 37°C with an automatic heating control unit. Regular checks of the viscosimeter were performed using standard oils with 3 different viscosities (PTB; Physical Technical Federal Institute, Braunschweig, Germany). The variability in repeated measurements was less than 1%. Fibrinogen was determined by immunonephelometry using the Behring Laser Nephelometer (Behringwerke, Marburg, Germany) with specific antibodies against human fibrinogen (OSCA 08/09; Behringwerke). Also in this assay, fragments of fibrin and fibrinogen are also detected; however, because of their very low concentration (<1 mg/L in nonthromboembolic and noninflammatory conditions), the results of the fibrinogen measurement are not influenced significantly.

Statistical Analysis

The results are reported as the mean ± SEM. Statistical analyses were performed with SPSS (SPSS Software, Munich, Germany) using the paired sample *t* test with a Bonferroni correction (for multiple testing) to compare fractions with native plasma. Pearson correlation coefficients were calculated to determine correlations between PV and the fibrinogen concentration in plasma and in each fraction. *P* values less than .05 were considered to indicate statistical significance.

RESULTS

In the first experiment, 7 hypercholesterolemic plasma samples were simultaneously pumped through 2 columns (fibrinogen-depleting and apolipoprotein B-100–depleting). After the fibrino-

gen-depleting column, the fibrinogen concentration decreased from 3.21 ± 0.20 to 0.94 ± 0.16 g/L ($P < .005$) in the first fraction, inducing a decrease in PV from 1.27 ± 0.02 to 1.17 ± 0.01 mPas (milliPascal seconds) ($P < .005$). However, total cholesterol remained unchanged (from 6.40 ± 0.23 to 6.23 ± 0.17 mmol/L). In each of the 7 samples, the fibrinogen concentration in all fractions and in plasma correlated well with PV (r between .84 and .97, $P < .02$, respectively) (Table 2). After the apolipoprotein B-100–depleting column, cholesterol was reduced from 6.40 ± 0.23 to 4.08 ± 0.32 mmol/L ($P < .005$) while PV (from 1.27 ± 0.02 to 1.24 ± 0.01 mPas) and the fibrinogen concentration (from 3.21 ± 0.20 to 3.10 ± 0.21 g/L) did not change significantly (Table 3).

In the second experiment, fibrinogen was removed from 7 hypertriglyceridemic plasma samples. The fibrinogen concentration in plasma (4.29 ± 0.79 g/L) and PV (1.42 ± 0.06 mPas) were elevated compared with the values in healthy subjects (normal fibrinogen 1.20 to 3.56 g/L and PV 1.18 to 1.40 mPas in our assays). The first fraction after the run-in period contained the lowest concentration of fibrinogen (1.62 ± 0.69 g/L) compared with the plasma fibrinogen level ($P < .001$), resulting in a decrease in PV to 1.03 ± 0.05 mPas ($P < .01$) in the first fraction after the column. Total triglycerides showed a slight and nonsignificant decrease after the column (from 19.13 ± 7.04 to 16.28 ± 5.15 mmol/L). Fibrinogen concentrations in plasma and fractions were significantly correlated with PV in 6 patients (r between .77 and .99, $P < .05$) and showed a trend to correlate in the seventh patient ($r = .62$, $P = .09$) (Table 4).

DISCUSSION

From epidemiological studies, fibrinogen has been suspected to be the most important determinant of PV.[7] In the 4,860 middle-aged men of the Caerphilly and Speedwell Collaborative Heart Disease Studies, the correlation coefficient between fibrinogen and PV was .57.[7] However, the results of simultaneous measurements of PV and serum viscosity in patients elucidate that fibrinogen alone seems to have only moderate effects on PV. In a population of nonsmokers, Lowe et al[8] found PV to be merely higher than serum viscosity (1.330 *v* 1.213 mPas). Thus, it seems obvious that other constituents of the plasma must contribute to PV, because the viscosity of pure water is only 0.69 mPas.[14]

The fibrinogen concentration showed a strong and consistent linear correlation with plasma viscosity in our in vitro study.

Table 2. Fibrinogen, Cholesterol, and PV After Fibrinogen-Depleting Column in Mildly Hypercholesterolemic Patients (n = 7, fractions compared with plasma concentration)

Fraction No.	Fibrinogen (g/L)	Cholesterol (mmol/L)	PV (mPas)
Plasma	3.21 ± 0.20	6.40 ± 0.23	1.27 ± 0.02
1	0.94 ± 0.16†	6.23 ± 0.17	1.17 ± 0.01†
2	1.27 ± 0.17†	6.29 ± 0.17	1.17 ± 0.01*
3	1.49 ± 0.17†	6.31 ± 0.16	1.18 ± 0.01†
4	1.60 ± 0.15†	6.32 ± 0.19	1.19 ± 0.01†
5	1.81 ± 0.17†	6.32 ± 0.18	1.20 ± 0.02*
6	1.87 ± 0.16†	6.29 ± 0.19	1.20 ± 0.02*

*$P < .01$.
†$P < .005$.

Table 3. Fibrinogen, Cholesterol, and PV After Apolipoprotein B-100–Depleting Column in Mildly Hypercholesterolemic Patients (n = 7, fractions compared with plasma concentration)

Fraction No.	Fibrinogen (g/L)	Cholesterol (mmol/L)	PV (mPas)
Plasma	3.21 ± 0.20	6.40 ± 0.23	1.27 ± 0.02
1	3.10 ± 0.21	4.08 ± 0.32*	1.24 ± 0.01
2	3.15 ± 0.22	4.51 ± 0.30*	1.23 ± 0.02
3	3.12 ± 0.20	4.69 ± 0.27*	1.25 ± 0.01
4	3.13 ± 0.22	4.89 ± 0.26*	1.25 ± 0.02
5	3.19 ± 0.21	4.94 ± 0.24*	1.25 ± 0.01
6	3.12 ± 0.19	5.04 ± 0.23*	1.24 ± 0.02

*$P < .005$.

One surprising finding is the low PV after fibrinogen depletion. This is in contrast to the results of previous studies in fibrinogen-free serum, where PV was reported to be only marginally lower versus fibrinogen-containing plasma.[14] In the 14 samples from the first and second experiments of our study, fibrinogen was reduced from 3.75 ± 0.42 to 1.28 ± 0.36 g/L, inducing a decrease in PV from 1.35 ± 0.04 to 1.11 ± 0.03 mPas. It may be hypothesized that PV decreased due to a dilution effect, but dilution was excluded because of the unchanged concentrations of cholesterol and triglycerides.

We believe that the relatively high viscosity in fibrinogen-free serum in other investigations might be due to an artificial effect, eg, related to the presence of microcomplexes of proteins (eg, fibrin) in the serum, which can be excluded by investigating plasma samples. This hypothesis would explain the inconsistency of a strong correlation between the fibrinogen concentration and PV in epidemiological studies while the viscosity of fibrinogen-free serum (fibrinogen concentration, 0 g/L) is only slightly lower than PV.

Epidemiological data indicate that the fibrinogen concentration correlates with the concentration of total cholesterol[15] and LDL cholesterol,[3-5] making it difficult to distinguish between the direct effect of lipoproteins and the effect of fibrinogen on PV. However, the direct effect of LDLs has also been investigated in vitro with conflicting results. Leonhardt et al[9] added isolated lipoprotein fractions to concentrated lipoprotein-free serum reconstituting the original volume by a Ringer solution. They found a weak association of the LDL concentration and PV only for very high LDL concentrations, suggesting a direct effect of LDLs. However, controversial results were found by Seplowitz et al.[10] They added isolated LDLs to lipoprotein-free

Table 4. Fibrinogen, Triglycerides, and PV After Fibrinogen-Depleting Column in Hypertriglyceridemic Patients (n = 7, fractions compared with plasma concentration)

Fraction No.	Fibrinogen (g/L)	Triglycerides (mmol/L)	PV (mPas)
Plasma	4.29 ± 0.79	19.13 ± 7.04	1.42 ± 0.06
1	1.62 ± 0.69†	16.28 ± 5.15	1.03 ± 0.05*
2	1.90 ± 0.86†	17.41 ± 5.86	1.22 ± 0.04*
3	2.26 ± 0.92†	17.54 ± 5.93	1.32 ± 0.05*
4	2.52 ± 0.92†	17.83 ± 5.97	1.34 ± 0.05†
5	2.69 ± 0.90†	18.12 ± 6.01	1.35 ± 0.05†
6	2.85 ± 0.92*	16.52 ± 5.15	1.33 ± 0.05*

*$P < .01$.
†$P < .001$.

plasma, resulting in a cholesterol concentration of 0 to 16.9 mmol/L. No significant influence on PV was found. One reason for the conflicting results might be the very high concentration of LDL used by Leonhardt et al. LDLs were concentrated from 200 to 1,500 mg/dL, representing a total cholesterol concentration of approximately 2.5 to 19.5 mmol/L. Our findings, as well as the results from Leonhardt et al[9] and Seplowitz et al,[10] suggest that physiologically concentrated or moderately elevated LDLs do not have a significant effect on PV.

Compared with controls, PV is higher in patients with hypertriglyceridemia[9] and chylomicronemia,[10] especially in the case of a marked elevation in triglycerides. In addition, in some epidemiological investigations, triglyceride levels were correlated with fibrinogen concentrations.[16] In our sample of hypertriglyceridemic patients, fibrinogen and PV were elevated. In our second experiment, PV became normal after the removal of fibrinogen from the plasma in these patients, suggesting that fibrinogen seems to be the main contributor to elevated PV in patients with marked hypertriglyceridemia. This is in good agreement with previous results, where we found PV and the fibrinogen concentration unchanged after a 52% decrease in triglycerides with gemfibrozil in patients with hypertriglyceridemia.[17] In contrast to our results, Stein and Rosenson[18] found a reduction in PV (−5.2%) and serum viscosity (−6.1%) during gemfibrozil therapy (triglyceride concentration, −70%) in hypertriglyceridemic patients, while the fibrinogen concentration showed a nonsignificant decrease (−9.3%). The reduction not only in PV but also in serum viscosity showed the decrease of viscosity to be independent from the fibrinogen concentration. However, in their study, the lowest posttreatment triglyceride, PV, and serum viscosity values from repeated measurements were chosen for analysis, which might result in a bias overestimating the reduction in PV and serum viscosity.

Our results confirm the association between the fibrinogen concentration and PV in patients with hypercholesterolemia and hypertriglyceridemia reported in epidemiological studies. The effect of the fibrinogen concentration on PV seems much more pronounced than the direct influence of lipoprotein concentrations. The elevated viscosity observed in patients with hypercholesterolemia and even in marked hypertriglyceridemia therefore seems mainly due to concomitantly elevated fibrinogen levels.

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