Relationship Between Plasma Viscosity and the Severity of Coronary Heart Disease

Ralf Junker, Jürgen Heinrich, Hans Ulbrich,† Helmut Schulte, Rainer Schönfeld, Ekkehart Köhler, Gerd Assmann

Abstract—Several studies have indicated that plasma viscosity contributes to cardiovascular risk in men. So far, a significant relationship between plasma viscosity and the severity of coronary heart disease has not been found. Thus, the present study is the first to report on the relationship of plasma viscosity and the severity of coronary heart disease. In a collective of 1142 male myocardial infarction patients, plasma viscosity and additional laboratory parameters were determined. Atherosclerotic changes were quantified by coronary angiography. Patients were divided into groups without any, and with one to three stenosed vessels. We found a positive relationship between plasma viscosity and the severity of coronary heart disease, even after adjusting groups for age, fibrinogen, and use of diuretics. Mean plasma viscosity ranged from 1.141±0.035 mPa s in patients without stenosed vessels to 1.162±0.044 mPa s in patients who had three coronary vessels with stenoses >50%. Differences between the groups were significant (P<0.001 to 0.05), with two exceptions: differences between patients without any and with one stenosed vessel, as well as between patients with one and two stenosed vessels, did not reach the significance level. On the whole, we can give further support to the hypothesis that cardiovascular risk factors and coronary heart disease may be linked by plasma viscosity. (Arterioscler Thromb Vasc Biol. 1998;18:870-875.)

Key Words: coronary heart disease ■ myocardial infarction ■ coronary risk factor ■ blood rheology ■ fibrinogen

In the prospective Caerphilly and Speedwell studies, as well as in the MONICA project, plasma viscosity was indicated as a predictive risk factor for CHD.1,2 In other studies, high plasma viscosity was shown to lead to an increased risk of acute MI in patients with unstable angina pectoris.3,4 Furthermore, a relationship of an early increase in plasma viscosity during acute MI and reinfarction or death was shown.5 An elevation of plasma viscosity was found in patients with severe unstable angina pectoris compared with patients with stable angina pectoris and to healthy individuals.6-8 Additionally, an elevated plasma viscosity in patients with stable angina pectoris,9 even without coronary artery stenosis at angiography,10 could be demonstrated. In the MONICA project, geographical differences in plasma viscosity between populations differing in the CHD event rates were found.11 Evidently, plasma viscosity contributes to the cardiovascular risk and may be of special importance in areas of reduced blood flow, as commonly occurs in patients with advanced atherosclerosis.12

Lowe et al13 suggested that blood viscosity is related to the extension of CHD. The study that proposed this suggestion, however, consisted only of a small group of patients, and therefore the results require further investigation. Moreover, in this study, plasma viscosity was not significantly elevated in patients with extensive CHD compared with a control group and to patients with less severe CHD. Thus, the present study is the first to report on the relationship of plasma viscosity and the severity of CHD in a large collective of 1142 male MI patients.

Methods

Patients

One thousand one hundred forty-two consecutive male MI patients, mean age 50.4±9.7 years, admitted to a coronary rehabilitation unit (LVA-Klinik Salzetal, Bad Salzuflen, Germany), were investigated. MI was diagnosed according to WHO criteria (central breast pain together with typical variations on electrocardiography or at least threefold increase of creatine kinase in the acute phase, or typical contraction disorder on angiography).14 Patients on oral anticoagulation were not included. There was no restriction on the use of antihypertensives, platelet aggregation inhibitors, and antidiabetics. Intake of lipid-lowering drugs was interrupted 2 weeks before blood sampling.

Evaluation of the Vascular Status

Investigation of the vessels and quantification of atherosclerotic changes were performed by physicians who were unaware of the laboratory results. Coronary angiography was performed by the
blood pressure
CHD = coronary heart disease
CRP = C-reactive protein
ELISA = enzyme-linked immunosorbent assay
F1 + 2 = prothrombin fragment 1 + 2
Lp(a) = lipoprotein(a)
MI = myocardial infarction
MLRA = multiple logistic regression analysis

standard femoral or brachial approach according to Judkins\textsuperscript{35} or Sones.\textsuperscript{16} The left main, as well as the left anterior descending, circumflex, and right coronary vessels, were studied. The left coronary artery was examined in several left anterior oblique views, including the craniocaudal projection, and at least three right anterior oblique views, including the craniocaudal projection. The right coronary artery was projected in at least one left anterior oblique view and two right anterior oblique views. To ensure that all vessel segments were viewed without an overlap, additional projections were recorded according to coronary morphology. Angiograms were recorded on 35-mm cineangiographic films or on laser discs. A coronary artery was classified to be affected by CHD if a stenosis of at least 50\% of diameter reduction at any segment was found by at least two observers. The severity of atherosclerosis was scored from 0 (no CHD) to 3 (stenosis >50\% in three vessels).

Blood Samples
Venous blood was drawn 4 to 6 weeks after MI. Within 2 hours after venipuncture, citrated plasma was separated by centrifugation at room temperature for 15 minutes at 2500g. Serum for clinical chemistry was prepared by centrifugation for 10 minutes at 3000g. After aliquots were deposited in plastic tubes, plasma and serum were immediately frozen and stored at −70°C.

Blood Analysis
Laboratory analyses were performed in one series at the Institute of Arteriosclerosis Research at the University of Münster, Germany, after having finished blood sample collection. Plasma viscosity was measured at 37°C using a falling ball viscosimeter (Microviscosimeter, Haake). Fibrinogen was determined on a KC10 coagulation analyzer (Amelung), according to Clauss,\textsuperscript{14} using thrombin, control plasma (both Behringwerke), and a plasma pool. D-Dimer concentrations were measured with an ELISA kit (Boehringer). Plasminogen and F1 + 2 were determined using chromogenic and ELISA kits, respectively, both by Behringwerke. CRP was measured using an ELISA kit (Eurogenetics). Measurement of total cholesterol and triglycerides in serum was performed on a Hitachi 737 autoanalyzer (Boehringer). HDL cholesterol concentrations were determined after precipitation with phosphotungstic acid/MgCl\textsubscript{2} (Boehringer) and LDL cholesterol was calculated using the Friedewald formula. Lp(a) concentrations were determined by means of electroimmunodiffusion with the use of standards and antiserum by Immuno.\textsuperscript{19}

Statistical Analysis
Nonnormally distributed variables were logarithmically transformed. Percentages of men with three and without any stenosed vessels, referring to the total number of patients within tertiles of plasma viscosity, were calculated. Age adjustment of patient groups was performed to minimize the effect of increasing age on the severity of CHD. Further statistical analysis was carried out after adjusting for age, levels of fibrinogen, and current use of diuretics. Age groups were <45, 46 to 50, 51 to 55, 56 to 60, and >60; cutoff levels for fibrinogen were <2.75, 2.76 to 3.30, and >3.30 g/L. Comparisons were made using t-tests and analysis of variance. Bivariate correlations were calculated according to Pearson. An MLRA was performed to examine the effects of different variables on plasma viscosity. All statistical analyses were performed using the SPSS\textsuperscript{4} package.

Results
Population Characteristics
Population characteristics are displayed in Table 1. Analysis of variance revealed a significant increase in mean values of different variables related to the number of stenosed coronary vessels (0 to 3): BP (systolic BP, 122.1 to 130.2 mm Hg, P<0.001; diastolic BP, 79.2 to 81.6 mm Hg, P<0.001), fibrinogen (2.79 to 3.31 g/L, P<0.001), plasminogen (92.5\% to 98.7\%, P<0.05), d-dimer (287.1 to 468.1 ng/mL, P<0.001), CRP (0.72 to 1.49 mg/L, P<0.001), and plasma viscosity (1.130 to 1.168 mPa s, P<0.001). In addition, the BMI was higher according to increasing severity of CHD (26.3 to 26.8 kg/m\textsuperscript{2}, P<0.05). Levels of lipids [total cholesterol, LDL and HDL cholesterol, triglycerides, and Lp(a)], as well as F1 + 2, were similar in patient groups. The percentage of smokers decreased according to an increase in the number of stenosed vessels (80.5\% to 51.7\%, P<0.05), whereas the percentage of men using diuretics was found to be higher with increasing severity of CHD (8.8\% to 32.3\%, P<0.001). The percentage of men using lipid-lowering drugs was similar in all CHD groups (Table 1).

Plasma Viscosity and Severity of CHD
The percentages of MI patients without any and with three stenosed vessels, referring to the total number of MI patients within tertiles of plasma viscosity, are shown in Figure 1. Tertile cutting points of plasma viscosity were 1.127 mPa s and 1.164 mPa s. The relative number of men with three stenosed vessels showed an increase according to higher levels of plasma viscosity (from 16.6\% within the lower tertile up to 32.7\% within the upper tertile). In contrast, the percentage of patients without stenosis of the coronary vessels decreased with higher levels of plasma viscosity (from 10.6\% within the lower tertile to 3.2\% within the upper tertile) (Figure 1).

Mean plasma viscosity was 1.135±0.042/1.141±0.035 mPa s (adjusted for age/age, fibrinogen, and use of diuretics) in MI patients without stenosed vessels (n=72), 1.145±0.041/1.147±0.038 mPa s with one stenosed vessel (n=467), 1.153±0.040/1.151±0.032 mPa s with two stenosed vessels (n=341), and 1.164±0.054/1.162±0.044 mPa s with three stenosed vessels (n=262).

With the exception of no versus one stenosed vessel, differences between the age-adjusted groups were significant (P<0.05 to P<0.001). After adjusting for age, fibrinogen, and use of diuretics, significance was lost for the difference between the groups with one and with two stenosed vessels (Figure 2).

Relationship Between Plasma Viscosity and Different Variables by Means of Bivariate Analysis and MLRA
Significant positive bivariate correlations were found between plasma viscosity and age, BMI, smoking, systolic BP, LDL cholesterol, triglycerides, fibrinogen, plasminogen, d-dimer, and CRP. Plasma viscosity and HDL cholesterol
were negatively correlated. With the exception of BMI and smoking ($P < 0.01$), probability was $< 0.001$ in all cases. No significant correlation was found between plasma viscosity and Lp(a) or $F_1$ $F_2$.

An MLRA was performed to consider the independence of the correlation between plasma viscosity and the variables investigated. All variables showing a significant bivariate correlation with plasma viscosity were taken into account. Significance remained for plasma viscosity and age, smoking, LDL cholesterol, triglycerides, fibrinogen, plasminogen, and CRP. With the exception of smoking and plasminogen ($P < 0.01$), probability was $< 0.001$ in all cases. Correlation was lost for plasma viscosity and BMI, systolic BP, HDL cholesterol, and $d$-dimer (Table 2).

### Discussion

This study is the first showing plasma viscosity to be related to the severity of CHD. Plasma viscosity showed a significant increase according to a higher number of stenosed coronary vessels in male MI patients.

In 1980, Lowe et al.\textsuperscript{13} suggested that blood viscosity is related to the extension of CHD. However, in the study proposing this suggestion, no significant relationship was found between plasma viscosity and the extension of CHD. The contrast to our results may be due to the fact that we investigated a larger collective. Geographical differences in plasma viscosity as described by Koenig et al.\textsuperscript{11} may also have contributed to different findings.

The strong positive correlation between plasma viscosity and fibrinogen found by other authors\textsuperscript{2,13,19–22} was confirmed by our results (Table 2). Because fibrinogen is the major determinant of plasma viscosity,\textsuperscript{23} patient groups were adjusted not only for age but also for levels of fibrinogen. Additionally, groups were adjusted for current use of diuretics to exclude an influence of such drugs. After this, the significant relationship between plasma viscosity and the severity of CHD remained and thus cannot be due to increased levels of fibrinogen or use of diuretics (Figure 2). Plasma viscosity was similar in patients using lipid-lowering drugs (until 2 weeks before blood collection) and patients not using these drugs (data not shown).

### Table 1. Population Characteristics of the 1142 Men Investigated Divided Into CHD Subgroups (0 to 3 Vessels Stenosed)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Stenosed Vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>72</td>
</tr>
<tr>
<td>Age, y</td>
<td>42.8±10.0</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>26.3±3.2</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>80.5</td>
</tr>
<tr>
<td>Current use of diuretics, %</td>
<td>8.8</td>
</tr>
<tr>
<td>Current use of lipid-lowering drugs, %</td>
<td>26.0</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>122.1±15.8</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>79.2±8.2</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.92±1.19</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>4.23±1.05</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.99±0.27</td>
</tr>
<tr>
<td>Triglycerides, mmol/L‡</td>
<td>0.72 (0.67–1.50)</td>
</tr>
<tr>
<td>Lp(a), g/L‡</td>
<td>140.1 (55.1–355.5)</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>2.79±0.67</td>
</tr>
<tr>
<td>Plasminogen, %</td>
<td>92.5±19.8</td>
</tr>
<tr>
<td>$F_1$ + 2, mmol/L‡</td>
<td>0.95 (0.50–1.80)</td>
</tr>
<tr>
<td>$d$-dimer, ng/mL‡</td>
<td>287.1 (137.2–543.9)</td>
</tr>
<tr>
<td>CRP, mg/L‡</td>
<td>0.72 (0.21–2.48)</td>
</tr>
<tr>
<td>Plasma viscosity, mPa s</td>
<td>1.130±0.042</td>
</tr>
</tbody>
</table>

Mean±SD or range are given. Results ($P$) of analysis of variance are shown in the last column.

* $P < 0.05$; † $P < 0.001$.

\textsuperscript{‡}Geometric mean.

### Figure 1. Percentages of MI patients without any and with three stenosed vessels referring to the total number of MI patients within tertiles of plasma viscosity.

![Figure 1](https://example.com/figure1.png)
In our study, the relative number of men with three stenosed vessels (referring to the total number of MI patients within tertiles of plasma viscosity) showed an increase according to higher levels of plasma viscosity, while the opposite was found for MI patients without stenosis of the coronary vessels (Figure 1). Elevated plasma viscosity has been shown to have a deleterious effect on oxygen delivery to the ischemic myocardium.24,25 An unfavorable blood flow may also lead to an increase in aggregation of blood cells, especially in the presence of high levels of fibrinogen.26,27 We therefore suggest that ischemia and a tendency to thrombosis in stenosed vessels due to a decreased blood flow with increasing viscosity contributes on the one hand to the progress of atherosclerosis. On the other hand, an increased cardiovascular risk through an elevated plasma viscosity may be of greater relevance in already stenosed coronary vessels.

Effects of rheological properties of blood on thrombogenesis and atherosclerosis have been summarized by several authors.12,28–30 Most of our findings concerning the relationship between plasma viscosity and other parameters were consistent with the results of other authors. The positive bivariate correlation between plasma viscosity and the acute-phase protein CRP remained significant in the MLRA. Acute-phase reactions are associated with the release of molecules of high molecular mass, which increase plasma viscosity. Hence, our findings support the assumption that atherosclerosis is a mild chronic inflammatory disease.31

A positive relationship between plasma viscosity and LDL cholesterol, as well as between plasma viscosity and triglycerides, which may be explained by rheological effects of molecules of high molecular mass, are consistent with the results of other studies.19,32–37 The negative bivariate correlation between plasma viscosity and HDL cholesterol seems to be equivocal but is nevertheless consistent with the findings of other authors.36–38 However, the relationship remained no longer significant after performing the MLRA.

Positive bivariate correlations between plasma viscosity and fibrinogen, as well as between plasma viscosity and plasminogen, remained significant in the MLRA, indicating an elevated hemostatic balance according to an increased plasma viscosity. No bivariate correlation was found between plasma viscosity and F1+2, whereas in the MLRA, significance was lost for the bivariate correlation between plasma viscosity and d-dimer. The latter results partly contrast the findings of Lowe et al,13 who suggested an imbalance of coagulation and fibrinolysis toward coagulation, but in their study fibrinopeptide A and fibrin Bβ1–42 were used as markers for coagulation and fibrinolysis. Fibrin Bβ1–42 is a degradation product of fibrinogen and non–cross-linked fibrin, whereas d-dimer results from plasmin-mediated fibrinolysis of cross-linked fibrin. As cross-linking is dependent on coagulation factor XIIIa, one may speculate that on the one hand, an increased plasma viscosity may increase factor XIII activity. On the other hand, cross-linking may be enhanced by an increased plasma viscosity. Fibrinopeptide A represents fibrin generation from fibrinogen, whereas F1+2 is a marker for thrombin generation. Levels of fibrinogen (and therefore nonadjusted levels of plasma viscosity) may be more closely

### Table 2. Relationship Between Plasma Viscosity and Different Variables by Means of Bivariate Analysis and MLRA

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.223</td>
<td>0.093</td>
</tr>
<tr>
<td>BMI</td>
<td>0.091</td>
<td>NS</td>
</tr>
<tr>
<td>Current smoker</td>
<td>−0.093</td>
<td>−0.080</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.145</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.160</td>
<td>0.131</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>−0.156</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.163</td>
<td>0.139</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.598</td>
<td>0.446</td>
</tr>
<tr>
<td>Plasminogen</td>
<td>0.076</td>
<td>0.069</td>
</tr>
<tr>
<td>F1+2</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>d-dimer</td>
<td>0.265</td>
<td>NS</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>0.458</td>
<td>0.174</td>
</tr>
</tbody>
</table>

r indicates Pearson correlation coefficient and β, multiple regression coefficient.

Performing MLRA, all parameters showing a significant bivariate correlation were taken into account. Positive correlations between plasma viscosity and variables can be attributed to molecules of high molecular mass (LDL cholesterol, triglycerides, CRP, fibrinogen, plasminogen, acute phase in smokers) or high white blood cell count (smokers).

*P<0.01; and †P<0.001.
related to fibrin generation than levels of thrombin, which might explain the differences in our findings.19

A causal relationship between BP and plasma viscosity may be suggested, but so far evidence has not been found. We can confirm a positive bivariate correlation as previously described,19,21,39,40 but no significant relationship between BP and plasma viscosity was found in the MLRA.

One of the linking mechanisms between smoking and CHD may be the increase in fibrinogen and white blood cell count in smokers and therefore an increase in plasma viscosity related to cigarette consumption.19,20,28,40 – 42 In our study, the proportion of smokers decreased according to the number of stenosed vessels (from 80.5% in patients without stenosed vessels to 51.7% in patients with three stenosed vessels). Hence, the relationship between smoking and CHD could neither be confirmed nor rejected.

Compared with the relevant literature, plasma viscosity values were low in our study (eg, Lowe et al,13 1.38±0.10 to 1.43±0.10 mPa s; Yarnell et al,2 1.688±0.096 to 1.735±0.099 mPa s; versus our results, 1.130±0.042 to 1.168±0.057 mPa s). Instead of the conventionally used EDTA-plasma, we used 1:10 diluted citrated plasma for measuring plasma viscosity. Therefore, this finding may be attributable to the dilution effect. Another aspect contributing to low plasma viscosity levels may be the storage of frozen plasma, which could lead to a breakdown of molecules of high molecular weight. Furthermore differences in methodology have to be taken into account when comparing results of different studies. However, as the above-mentioned aspects would lead to a systematic shift in the viscosity values, the conclusions of our study are not influenced by them.

On the whole, with our recent findings, we can give further support to the hypothesis that an increased plasma viscosity may be a linking mechanism between cardiovascular risk factors and CHD. Clinical studies will be required to investigate the therapeutic benefit of reducing plasma viscosity in the clinical management of CHD.

Acknowledgments

This study was supported by the Bundesministerium für Forschung und Technologie, the Ministerium für Wissenschaft und Forschung NRW, the Deutsche Forschungsgemeinschaft, the Landesversicherungsanstalt Westfalen, and the Landesversicherungsanstalt Rheinprovinz. The excellent technical cooperation of R. Baümer, M. Rütten, M. Rehls-R Seeßle, and R. Baümer is gratefully acknowledged. We thank F. Stuhlreiter for English editing.

References


Relationship Between Plasma Viscosity and the Severity of Coronary Heart Disease
Ralf Junker, Jürgen Heinrich, Hans Ulbrich, Helmut Schulte, Rainer Schönfeld, Ekkehart Köhler and Gerd Assmann

*Arterioscler Thromb Vasc Biol.* 1998;18:870-875
doi: 10.1161/01.ATV.18.6.870

*Arteriosclerosis, Thrombosis, and Vascular Biology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/18/6/870

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Arteriosclerosis, Thrombosis, and Vascular Biology* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Arteriosclerosis, Thrombosis, and Vascular Biology* is online at:
http://atvb.ahajournals.org/subscriptions/