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Wolfgang Koenig, Malte Sund, Birgit Filipiak, Angela Döring, Hannelore Löwel and Edzard
Ernst

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Plasma Viscosity and the Risk of Coronary Heart Disease

Results From the MONICA-Augsburg Cohort Study, 1984 to 1992

Wolfgang Koenig, Malte Sund, Birgit Filipiak, Angela Döring,
Hannelore Löwel, Edzard Ernst

Abstract—Plasma viscosity is determined by various macromolecules, eg, fibrinogen, immunoglobulins, and lipoproteins. It may therefore reflect several aspects involved in cardiovascular diseases, including the effects of classic risk factors, hemostatic disturbances, and inflammation. We examined the association of plasma viscosity with the incidence of a first major coronary heart disease event (CHD; fatal and nonfatal myocardial infarction and cardiac death; $n=50$) in 933 men aged 45 to 64 years of the MONICA project of Augsburg, Germany. The incidence rate was 7.23 per 1000 person-years (95% confidence interval [CI], 5.37 to 9.53), and the subjects were followed up for 8 years. All suspected cases of an incident CHD event were classified according to the MONICA protocol. There was a positive and statistically significant unadjusted relationship between plasma viscosity and the incidence of CHD. The relative risk of CHD events associated with a 1-SD increase in plasma viscosity ($0.070 \text{ mPa} \cdot \text{s}$) was 1.60 (95% CI, 1.25 to 2.03). After adjustment for age, total cholesterol, high density lipoprotein cholesterol, smoking, blood pressure, and body mass index, the relative risk was reduced only moderately (1.42; 95% CI, 1.09 to 1.86). The relative risk of CHD events for men in the highest quintile of the plasma viscosity distribution in comparison with the lowest quintile was 3.31 (95% CI, 1.19 to 9.25) after adjustment for the aforementioned variables. A large proportion of events (40%) occurred among men in the highest quintile. These findings suggest that plasma viscosity may have considerable potential to identify subjects at risk for CHD events. (*Arterioscler Thromb Vasc Biol.* 1998;18:768-772.)

Key Words: viscosity ■ plasma ■ coronary heart disease ■ incidence ■ prospective studies

Positive associations of various factors, like smoking, blood pressure, and cholesterol, with the incidence of CHD are well established. However, high-risk patients identified by hypertension, smoking, and elevated cholesterol accounted for only 32% of all future MIs in one study.¹ Furthermore, event rates vary considerably across countries, a fact that cannot be explained by differences in conventional risk factors.^{2,3} Plasma viscosity, a major determinant of blood flow in the microcirculation, may be one explanation of such a difference.⁴ Thus, other factors might contribute to the pathogenesis of CHD. Evidence from prospective studies has implicated fibrinogen as a major independent cardiovascular risk factor.⁵

Only three prospective studies are available wherein plasma viscosity (which is determined to some extent by fibrinogen) was measured along with other risk-related parameters. Plasma viscosity, as well as fibrinogen and white blood cell count, was positively associated with the incidence of CHD events in a population-based study of middle-aged men.^{6,7} Plasma viscosity and fibrinogen were also associated

with incident CHD and stroke in a study of older men and women⁸ and with recurrence of stroke in another study.⁹

In the first cross-sectional study of the MONICA Project, Augsburg, 1984 to 1985, plasma viscosity but not fibrinogen was measured in addition to conventional risk factors. This report assesses the prognostic impact of plasma viscosity for a first major incident CHD event in 45- to 64-year-old German men.

Methods

MONICA Project, Augsburg

The objectives and design of the MONICA Project have been described elsewhere.^{10,11} The first cross-sectional study of the MONICA-Augsburg center was carried out in 1984 and 1985, and details of the study population, sampling frame, and data collection procedures have also been published.¹²⁻¹⁴ In brief, 4022 of the 5069 eligible individuals, aged 25 to 64 years old, who were initially sampled at random from a study population of 282 279 inhabitants of a mixed urban/rural area participated in the study (response rate, 79.3%).

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From the Department of Internal Medicine II, Cardiology, University of Ulm Medical Center, Ulm, Germany (W.K.); the GSF National Research Center for Environment and Health, MEDIS Institute (M.S.) and Institute of Epidemiology (B.F., A.D., H.L.), Neuherberg, Germany; and the Postgraduate Medical School (E.E.), University of Exeter, Exeter, UK.

Correspondence to Wolfgang Koenig, MD, Department of Internal Medicine II, Cardiology, University of Ulm Medical Center, Robert-Kochstrasse 8, D-89081 Ulm, Germany.

E-mail wolfgang.koenig@medizin.uni-ulm.de

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Selected Abbreviations and Acronyms

- (A)MI = (acute) myocardial infarction
 CHD = coronary heart disease
 CI = confidence interval
 MONICA = MONItoring trends and determinants in
 Cardiovascular disease
 RR = relative risk

The present report is based on all men, aged 45 to 64 years, who participated in the first survey (N=1074). Of these subjects, 43 were excluded because of a previous MI. Eight were excluded due to their medical history suggesting a disease other than CHD. In the remaining 1023 men, measurements of plasma viscosity were missing from 79 individuals (7.7%); in 11 additional men, at least one control variable could not be obtained. Thus, a total of 933 men aged 45 to 64 years with data on all variables were studied.

Survey and Laboratory Methods

Participants completed a standardized questionnaire including medical history, lifestyle, and drug history.¹² Blood pressure, body height (in meters), body weight (in kilograms), body mass index (weight divided by the square of height), and smoking behavior were determined as described elsewhere.^{15,16}

Nonfasting blood samples were drawn and prepared according to the recommendations of the International Committee for Standardization in Hematology.¹⁷ EDTA-blood was centrifuged at 3000g for 15 minutes. A Harkness Coulter viscometer (Coulter Electronics) was used to measure plasma viscosity at 37°C.¹⁸ Plasma viscosity (millipascal-seconds) tests were done in triplicate. For quality control, measurements were compared daily with those of water. The coefficient of variation was 1.0%. At irregular intervals, duplicates were measured in single-blind fashion. Their coefficient of variation was 2.0%, and 93% of the duplicates differed by <5%. Total and HDL cholesterol levels were measured by enzymatic methods.

Follow-up Procedures

Within the population-based coronary event register, which is part of the MONICA Project, all death certificates for residents of the study area aged 25 to 74 years have been continuously screened for suspected cases of AMI since October 1, 1984. Additional information was gained from standardized questionnaires sent to general practitioners and/or to the coroner. Based on information from both the death certificate and the questionnaire, the register team decided whether a case fulfilled the MONICA algorithm for fatal CHD. Data on in-hospital cases of fatal and nonfatal AMI were collected actively by registered nurses. No information could be obtained on unhospitalized nonfatal events (<1% of AMI patients). The case-finding procedure and data quality aspects have been published in detail elsewhere.^{19,20} At 2-year intervals, addresses of all participants of the first survey in 1984 and 1985 were checked and information on vital status was collected. If a subject had died, information on the cause of death was obtained. We report the results of the 8-year follow-up of participants of the first survey (as of December 31, 1992).

Statistical Methods

An incident event was defined as a first-ever fatal or nonfatal AMI, including sudden cardiac death. According to the MONICA Manual,²¹ the diagnosis of a major CHD event was made on the basis of the patients' symptoms, cardiac enzymes (creatinine phosphokinase, aspartate aminotransferase, and lactate dehydrogenase), serial changes on a 12-lead electrocardiogram evaluated by Minnesota coding,²² necropsy results, and a history of CHD in fatal cases.

Plasma viscosity was used as a continuous variable and was also categorized into quintiles. Preliminary analyses showed that quadratic and cubic terms did not have any appreciable effects. Variables investigated for possible confounding effects were age (the

four 10-year age groups of the basic sampling design), body mass index (categorized according to Bray¹⁶), total cholesterol (cut points recommended by the National Heart, Lung, and Blood Institute Consensus Conference²³), HDL cholesterol (<0.9 mmol/L or ≥0.9 mmol/L), hypertension (World Health Organization categories), and smoking status (never-smoker, ex-smoker, or current smoker). Adjusted RRs of a first major incident CHD event for increased plasma viscosity were computed by fitting Cox proportional-hazards models to the event-free times. All computations and graphical work were done with the help of SAS software, version 6.11 for Windows 3.1.²⁴ Statistical tests were performed at a nominal 5% level.

Results

During follow-up, 50 first major incident CHD events (5.4%) occurred in the cohort of 933 men aged 45 to 64 years. There were 25 nonfatal and 25 fatal events. The average annual incidence rate for a first AMI was 7.23 per 1000 person-years (95% CI, 5.37 to 9.53). Maximum observation time was 8.2 years.

The distributions of the risk variables did not differ appreciably between the study sample and the initial 1074 male participants. Table 1 presents the categorical risk variables with their group frequencies, number of CHD events, plasma viscosity means, and *P* values testing the simultaneous equality of the means of a given variable. All variables except HDL cholesterol showed a positive and graded relation with plasma viscosity, HDL cholesterol being negatively related. Thus, all variables exhibited increasing plasma viscosity levels with increasing severity of the risk variable. These variables were therefore included in subsequent regression analyses.

Fig 1 shows a plot of the estimated survival distribution functions (Kaplan-Meier) of the time to a first major incident event of CHD stratified by plasma viscosity quintiles. The plot indicates that the first four quintiles can hardly be distinguished, whereas the fifth quintile (1.34 to 1.56 mPa · s) is well separated from the rest. The top quintile's survival-function values were at all times >2 years, considerably smaller than those of the other quintiles, suggesting an inverse association of the time to event with plasma viscosity.

Fig 2 summarizes Cox regressions with plasma viscosity categorized into quintiles. The graph shows the risk of the plasma viscosity quintiles, relative to the first quintile, both unadjusted and adjusted for all covariables together with 95% CIs. Here, too, the similarity of the first four quintiles at a low level and the much higher level of the top quintile can be noted. Compared with the first quintile, the top quintile had an unadjusted RR of 4.17 (95% CI, 1.79 to 12.72) which, after adjustment for all covariables, decreased to 3.31 (95% CI, 1.19 to 9.25). Compared with the combined first four quintiles, the fifth quintile had an adjusted RR of 2.68 (95% CI, 1.48 to 4.88).

Table 2 summarizes Cox regressions relating plasma viscosity as a continuous variable to the incidence of a first major CHD event, both unadjusted and adjusted for age and for all covariables. The table contains regression coefficients, their SEs, corresponding *P* values, standardized regression coefficients, and RRs for all variables used in the regressions. RRs for the categorical variables are relative to first categories. The unadjusted RR of CHD events for a 1-SD increase

TABLE 1. Categorical Covariables With Group Frequencies, Number of CHD Events, and Plasma Viscosity Means: MONICA-Augsburg Cohort Study, 1984 to 1992

Variable*	Group	Frequency, %	Number of CHD Events	Plasma Viscosity Mean, mPa · s	SEM, mPa · s	P†
Age	45–54 Years	51.8	18	1.268	0.003	.012
	55–64 Years	48.2	32	1.280	0.003	
BMI	<25 kg/m ²	19.6	12	1.261	0.005	<.001
	25–29.9 kg/m ²	58.8	28	1.273	0.003	
	≥30 kg/m ²	21.5	10	1.289	0.005	
TC	<5.2 mmol/L	16.4	4	1.252	0.005	<.001
	5.2–6.2 mmol/L	32.7	14	1.258	0.004	
	≥6.1 mmol/L	50.9	32	1.291	0.003	
HDL	<0.9 mmol/L	11.6	4	1.297	0.007	<.001
	≥0.9 mmol/L	88.4	46	1.271	0.002	
Smk	Never-smoker	26.2	8	1.258	0.004	<.001
	Ex-smoker	40.8	14	1.270	0.004	
	Current smoker	33.0	28	1.292	0.004	
BP	<140/90 mm Hg	53.3	22	1.264	0.003	<.001
	Otherwise	26.0	14	1.276	0.004	
	≥160/95 mm Hg	20.7	14	1.296	0.005	

N=933, men age 45–64.

*BMI indicates body mass index; TC, total cholesterol; HDL, HDL cholesterol; Smk, smoking; and BP, blood pressure.

†P value for testing the equality of all the means of a given variable.

(0.070 mPa · s) in plasma viscosity was 1.60 (95% CI, 1.25 to 2.03). Adjustment for age decreased it only slightly to 1.56. Adjustment for all covariables decreased the value further but left a substantial and statistically significant RR of 1.42 (95% CI, 1.09 to 1.86). The standardized regression coefficients were obtained by multiplying each regression coefficient by 1 SD of the corresponding variable. They thus facilitate the assessment of the relative importance of the variable in the regression model.

Discussion

This study shows a positive and independent association between plasma viscosity and a first major incident CHD event in middle-aged men randomly drawn from a general population. Consistent, positive, and statistically highly sig-

nificant associations existed between conventional risk factors and plasma viscosity, except for HDL cholesterol, which was inversely related (Table 1). When all of these variables were taken into account, the association between plasma viscosity and CHD events remained substantial (Table 2).

Yarnell et al⁶ investigated >4800 middle-aged men in two communities in Wales and England (Caerphilly and Speedwell studies) and followed them up for 5.1 and 3.2 years, respectively. This study and the present cohort analyzed men in the same age range and determined plasma viscosity by the same instrument with the same high reproducibility.^{4,6} There are, however, some differences with regard to end-point determination. The Caerphilly and Speedwell Collaborative Heart Disease Studies also included silent MI due to the availability of

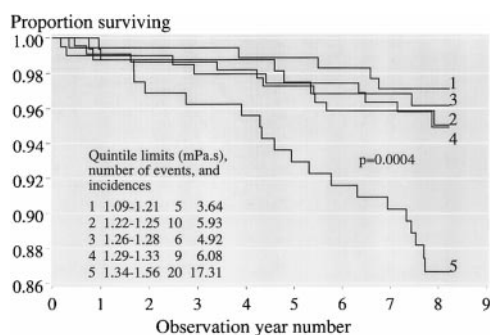


Figure 1. Graph showing the survival distribution functions of the time to a first major incident event of CHD by plasma viscosity quintiles. Also given are quintile limits, the number of CHD events, incidence rates per 1000 person-years, and the P value of the log-rank test testing the equality of the survival functions. MONICA-Augsburg Cohort Study 1984–1992. N=933 men aged 45 to 64 years.

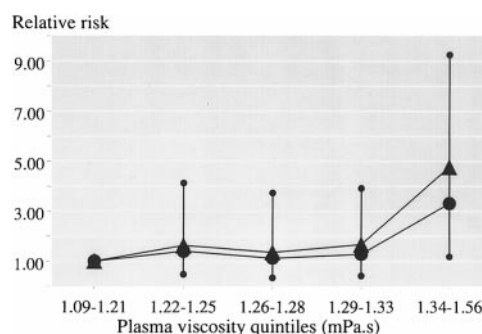


Figure 2. Graph showing the RR of a first major incident event of CHD by plasma viscosity quintiles, relative to the first quintile. Shown are unadjusted RRs (filled triangle); RRs adjusted for age, smoking behavior, total and HDL cholesterol, blood pressure, and body mass index (filled circle); and 95% CIs for the adjusted RR (filled circle with line). Quintiles are indicated with their limits. MONICA-Augsburg Cohort Study 1984–1992. N=933 men aged 45 to 64 years.

TABLE 2. Cox Regressions of CHD on Plasma Viscosity: MONICA-Augsburg Cohort Study, 1984 to 1992

Adjustment	Variable*	Group	Regression Coefficient, b^{\dagger}	SE	P	Standardized Regression Coefficient, $b \cdot s^{\ddagger}$	RR§	95% CI
None	PV	mPa · s	6.708	1.773	<.001	0.467	1.60	1.25–2.03
Age	PV	mPa · s	6.356	1.778	<.001	0.443	1.56	1.22–1.99
	Age	45–54 Years						
		55–64 Years	0.589	0.296	.047	0.294	1.80	1.01–3.22
All covariables	PV	mPa · s	5.083	1.947	.009	0.354	1.42	1.09–1.86
	Age	45–54 Years						
		55–64 Years	0.611	0.299	.041	0.305	1.84	1.03–3.31
	BMI	<25 kg/m ²						
		25–29.9 kg/m ²	−0.411	0.354	.246	−0.202	0.66	0.33–1.33
		≥30 kg/m ²	−0.509	0.445	.253	−0.209	0.60	0.25–1.44
	TC	<5.2 mmol/L						
		5.2–6.1 mmol/L	0.510	0.569	.370	0.240	1.67	0.55–5.09
		≥6.2 mmol/L	0.707	0.537	.188	0.354	2.03	0.71–5.81
	HDL	<0.9 mmol/L						
		≥0.9 mmol/L	0.535	0.529	.312	0.171	1.71	0.61–4.82
	Smk	Never-smoker						
		Ex-smoker	−0.109	0.452	.809	−0.054	0.90	0.37–2.17
		Current smoker	0.822	0.409	.045	0.387	2.27	1.02–5.07
	BP	<140/90 mm Hg						
		Otherwise	0.253	0.347	.467	0.111	1.29	0.65–2.54
		≥160/95 mm Hg	0.434	0.361	.229	0.176	1.54	0.76–3.13

N=933, Men, age 45–64.

*PV indicates plasma viscosity; BMI, body mass index; TC, total cholesterol; HDL, HDL cholesterol; Smk, smoking; and BP, blood pressure.

†For PV, compute RR for an arbitrary PV difference d from b as $RR = \exp(d \cdot b)$ and the CI limits as $\exp[d \cdot (b \pm 1.96 \cdot s)]$. The b for the categorical variables are relative to the first categories.‡ b multiplied by the SD of the variable to make the variables comparable.

§For PV computed for 1 SD (0.070 mPa · s).

sequential electrocardiograms, which was not possible in the MONICA-Augsburg population. Furthermore, in contrast to the present study, Yarnell et al⁶ recruited a high proportion of patients with prevalent CHD and made adjustments for this factor in multivariate analysis. Both studies used rigid criteria for the diagnosis of AMI. The adjusted RR of a first major incident CHD event for an increase in plasma viscosity by 1 SD (0.096 mPa · s at 25°C, equivalent to ≈ 0.072 mPa · s at 37°C) in the Caerphilly and Speedwell Collaborative Heart Disease Studies was 1.33 (using their model 2 but excluding fibrinogen and white blood cell count; P.M. Sweetnam, personal communication, 1996). This RR was similar to the one we found with our model in the present study, namely, 1.42 (95% CI, 1.09 to 1.86) for an increase in plasma viscosity by 1 SD (0.070 mPa · s). Our quintile limits are lower than those in the report of Yarnell et al,⁶ but for all quintiles by the same amount (0.05 mPa · s in Caerphilly and 0.02 mPa · s in Speedwell; J.W.G. Yarnell, personal communication, 1996). Therefore, our plasma viscosity distribution is similar in shape but shifted to the left of that in Yarnell et al and in the Glasgow MONICA Study.⁴ Our results, therefore, support the findings of Yarnell et al of a positive association of considerable size of plasma viscosity with incident CHD, independent of other conventional risk factors. Similar findings were also recently reported from the Edinburgh Artery Study cohort of men and women aged 55 to 74 years.⁸

To date, several prospective studies have convincingly documented an association between fibrinogen and CHD.⁵ In some of these analyses, an association with stroke (Gothenburg Study, Framingham Study⁸) was also reported. In another study, the degree of abnormality of plasma viscosity and fibrinogen during stroke rehabilitation (ie, after the acute-phase response had subsided) was related to the 2-year prognosis of these patients.⁹ The association between plasma viscosity and incident CHD and stroke is partly ($\approx 50\%$) explained by their mutual associations with fibrinogen.⁷

Plasma viscosity can be measured quickly, cheaply, and reproducibly.²⁵ Furthermore, it shows only minimal intraindividual variability.²⁵ Thus, this parameter has advantages over the measurement of fibrinogen. A considerable part of the relation of fibrinogen to the occurrence of cardiovascular events might be attributable to its effect on plasma viscosity. Plasma viscosity directly determines blood flow at the microcirculatory level,²⁶ and plasma hyperviscosity results in a deterioration of microcirculatory blood flow, which theoretically limits tissue perfusion, in particular in poststenotic areas with low shear forces. Thus, one might argue that hyperfibrinogenemia, at least in part, conveys a risk for subsequent CHD events by its negative influence on the flow properties of blood.²⁷ The only study so far that has measured both variables to assess the risk for future

CHD events was not able to clearly differentiate between the two.⁶ The 10-year follow-up from the Caerphilly and Speedwell Studies confirmed their initial results and found that plasma viscosity remained a predictor of risk at every level of fibrinogen and vice versa.

For a group of 274 healthy men aged 25 to 64 years (no cardiovascular or other chronic diseases and no cardiovascular risk factors) drawn from the same population as our study sample, the mean plasma viscosity value was $1.23 \text{ mPa} \cdot \text{s}$, with an SD of $0.05 \text{ mPa} \cdot \text{s}^{25}$, such that the upper limit of a reference range (mean plus 2 SD) can be estimated as $1.33 \text{ mPa} \cdot \text{s}$ (given that plasma viscosity is measured at 37°C). Fig 2 suggests a dichotomy in plasma viscosity values, the cutoff point being at just the upper limit of the reference range, ie, $1.33 \text{ mPa} \cdot \text{s}$. For this dichotomy, we found an RR of 2.68 (95% CI, 1.48 to 4.88); ie, plasma viscosity values $>1.33 \text{ mPa} \cdot \text{s}$ were associated with an increase for CHD risk of 168%. This magnitude of increase in CHD risk is generally considered substantial.

The fact that plasma viscosity is also influenced by other acute-phase proteins, like α_2 -macroglobulin, certain immunoglobulins, and large lipoproteins, renders it a biochemically composite variable. There is evidence to suggest that the hepatic synthesis of fibrinogen is triggered by various mediators involved in the early stages of atherogenesis and in its clinical complications. In particular, the production and secretion of interleukin-6, the major cytokine of the acute-phase response, is stimulated by damaged endothelial cells, fibroblasts, and activated monocytes and macrophages.²⁸ Increased plasma viscosity therefore may be an easily accessible marker of early atherosclerosis. It could serve as a new parameter identifying those individuals at risk for clinically important cardiovascular complications and might be superior to the measurement of any single acute-phase protein. Plasma viscosity may also be one mechanism through which elevated lipoproteins may promote ischemic events.^{29,30} For all of these reasons, we suggest that plasma viscosity merits further studies as a predictor of cardiovascular risk.

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