Whole-blood viscosity and the insulin-resistance syndrome

Aud Høieggen, Eigil Fossum, Andreas Moan, Erik Enger and Sverre E. Kjeldsen

Background **In a previous study we found that elevated blood viscosity was linked to the insulin resistance syndrome, and we proposed that high blood viscosity may increase insulin resistance. That study was based on calculated viscosity.**

Objective **To determine whether directly measured whole-blood viscosity was related to the insulin-resistance syndrome in the same way as calculated viscosity had been found to be.**

Methods **Healthy young men were examined with the hyperinsulinemic isoglycemic glucose clamp technique, and we related insulin sensitivity (glucose disposal rate) to other metabolic parameters and to blood viscosity. We established a technique for direct measurement of whole-blood viscosity.**

Results **There were statistically significant negative correlations between glucose disposal rate and whole-blood viscosity at low and high shear rates ($r = -0.41$, $P = 0.007$ for both, $n = 42$). Whole-blood viscosity was correlated positively ($n = 15$) to serum triglyceride ($r = 0.54$, $P = 0.04$) and total cholesterol ($r = 0.52$, $P = 0.05$), and negatively with high-density lipoprotein cholesterol ($r = -0.53$, $P = 0.04$) concentrations. Insulin sensitivity index was correlated positively to high-density lipoprotein cholesterol ($r = 0.54$, $P = 0.04$) and negatively to serum triglyceride ($r = -0.69$, $P = 0.005$) and to total cholesterol ($r = -0.81$, $P = 0.0003$) concentrations.**

Conclusions **The present results demonstrate for the first time that there is a negative relationship between directly measured whole-blood viscosity and insulin sensitivity as a part of the insulin-resistance syndrome. Whole-blood viscosity contributes to the total peripheral resistance, and these results support the hypothesis that insulin resistance has a hemodynamic basis. *J Hypertens* 16:203–210 © 1998 Rapid Science Ltd.**

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Department of Internal Medicine, Ullevaal Hospital, University of Oslo, Oslo, Norway.

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Requests for reprints to Dr Aud Høieggen, Department of Internal Medicine, Ullevaal Hospital, N-0407 Oslo, Norway.

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Introduction

Resistance to insulin stimulated glucose disposal has been detected in subjects with essential hypertension [1,2] and has been proposed to be a metabolic link among noninsulin-dependent diabetes mellitus, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease [3,4]. The primary site of insulin resistance, measured by the glucose-clamp technique, is skeletal muscle [5]. Several reports have suggested that there is an association between disturbances in blood flow and insulin-stimulated uptake of glucose, and recently Julius *et al.* [6] proposed that there is a hemodynamic link between insulin resistance and hypertension. Laakso *et al.* [7] showed that there is a lower increment in blood flow to skeletal muscle during hyperinsulinemic glucose clamping in obese insulin-resistant individuals than there is in insulin-sensitive controls. A lower post-prandial blood flow to skeletal muscle [8] and lower capillary density [9] are also associated with insulin resistance.

It has been suggested in many reports that whole-blood viscosity is an independent risk factor for cardiovascular disease [10–12] and peripheral vascular disease [13], and it is a correlate both of systolic and of diastolic blood pressure (DBP) [14]. During the last few years many reports have been published on changes in viscosity, hematocrit level, and other hemorheological factors in diabetes and hypertension. We suggested recently that elevated blood viscosity could be part of the insulin-resistance syndrome [15,16], and that high blood viscosity might by itself increase insulin resistance. Our previous results [15,16] were based on calculated viscosity [17]. We have now established a technique for direct measurements of whole-blood viscosity. The present study was designed to test our hypothesis that there is a relationship between insulin sensitivity and whole-blood viscosity as a part of the cardiovascular metabolic syndrome by using this new technique.

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The concept that lipoproteins are contributors to insulin resistance is well established. High serum triglycerides and total cholesterol and low high-density lipoprotein (HDL) cholesterol concentrations are parts of the insulin-resistance syndrome [18]. The correlation between lipoprotein concentrations and whole-blood viscosity also seemed to be uniform in previous studies [17–21]. Total cholesterol and serum triglycerides cause rigidification of erythrocytes because of metabolic relations between lipoprotein functions and cell membranes [17–21]. Rigidity of erythrocytes contributes to higher viscosity, especially in the microcirculation [17–22].

We examined 15 healthy young men with the hyperinsulinemic isoglycemic glucose clamp technique, and related our results to other metabolic parameters and whole-blood viscosity. To increase the statistical power regarding the relationship between insulin sensitivity and viscosity at a high shear rate, we expanded the material by using data from 27 subjects of a subsequent series of young men recruited from the same population and studied in our laboratory using the same methods in the same experimental setting. We also aimed at examining the stability of directly assessed whole-blood viscosity during clamping and whether it is influenced by the clamp procedure itself.

Subjects and methods

Subjects

We examined 21-year-old Caucasian men recruited from the records after the medical examination during the military draft procedure in the city of Oslo. Attending is compulsory, and only men with severe medical disorders do not attend. Therefore, the population comprises all healthy 18-year-old men in the Oslo area (yearly approximately 3500 men). Heart rate, body weight, height and sitting blood pressure were recorded. No follow-up of the subjects was performed until the present study was undertaken 3 years later.

In 1994, we invited men (n = 36) who had had DBP higher than 90 mmHg on one occasion (i.e. during the medical examination of the military draft procedure in 1991) to attend a screening for cardiovascular risk factors at Ullevaal Hospital. Of these, 15 men were willing to participate in the present study. They underwent a thorough physical examination, blood biochemistry measurements including renal and liver functioning tests, and urinalysis to exclude the possibility that they had illnesses including diabetes mellitus. They were all considered healthy and none was using or had ever used medications regularly. At baseline in the laboratory only two of them had DBP > 90 mmHg. All subjects fasted and refrained from smoking for at least 10 h, and abstained from drinking alcohol for the last 24 h before the study. Otherwise they had a free diet and activity regimen prior to being studied. Only two subjects reported that they were regular smokers, and exclusion of their data from the analysis did not affect the results. Body mass index (BMI) averaged 25.2 ± 0.8 kg/m^2 (range 20.4–30.7), supine heart rate 65 ± 3 beats/min (50–97), and supine blood pressures $136 \pm 4/77 \pm 2$ mmHg (117–189/61–100). The degrees of central obesity and family histories of hypertension were not assessed. The study was approved by the ethics committee of Health Region No. 1, Norway, and their informed consent to participate in the study was obtained from each subject.

Characteristics for the 27 additional subjects subsequently included to increase the statistical power for the relationship between insulin sensitivity and whole-blood viscosity at high shear rate were the same. Thus mean ± SEM values for BMI, supine heart rate, and blood pressure were almost identical to those of the first 15 subjects.

Glucose-clamp examination

An antecubital vein on the right arm was cannulated with a short Teflon catheter (Venflon 17G, Viggo AB, Hälsingborg, Sweden) and the right forearm was then placed in a heating sleeve (Thermal Vascular Dilatator, Swetron AB, Veddesta, Sweden). The temperature was set at 52.0°C, and the right arm was thus used for sampling of arterialized venous blood. The heating of the arm indirectly increases the blood flow, and imitates the blood in the arteries. This is done to obtain the best estimate of arterial blood concentrations of glucose, the stimulus to pancreatic insulin secretion. An antecubital vein on the left arm was also cannulated with a short Teflon catheter (Venflon 18G) for later infusion of insulin and glucose. The subjects then rested supine for 20 min in the presence of the examining physician before recordings of baseline blood pressure and heart rate, and blood sampling.

The isoglycemic hyperinsulinemic glucose clamp was thereafter performed using a modification of the method described by DeFronzo *et al.* [23]. Insulin was infused at a fixed rate of 1 mU/kg per min. Blood glucose concentration was clamped at the subject's fasting level (isoglycemia); this was obtained by measuring glucose concentration every 5 min and adjusting the rate of an intravenous infusion of glucose (concentration 240 mg/ml) according to the results. Isoglycemia was maintained for 120 min and the glucose disposal rate (GDR) was calculated from the amount of glucose infused during the last 20 min. Average plasma insulin level during the clamp was 758 ± 67 pmol/l. Because of individual differences in metabolic rate of insulin clearance and possible continuation of endogenous insulin secretion, the steady-state levels of insulin varied from one person to another. We therefore also calculated the insulin-sensitivity index (ISI) [23], which is a measure of the sensitivity of tissue to the attained insulin concentration [i.e. the amount of glucose metabolized per unit of serum insulin (GDR divided by

mean level of insulin during the last 20 min of clamping, mg/kg body weight per min per pmol per l multiplied by 100 arbitrary units; GDR/I)]. This technique for measuring the glucose disposal rate has a day-to-day coefficient of variation of less than 5% in our laboratory.

Analytic methods

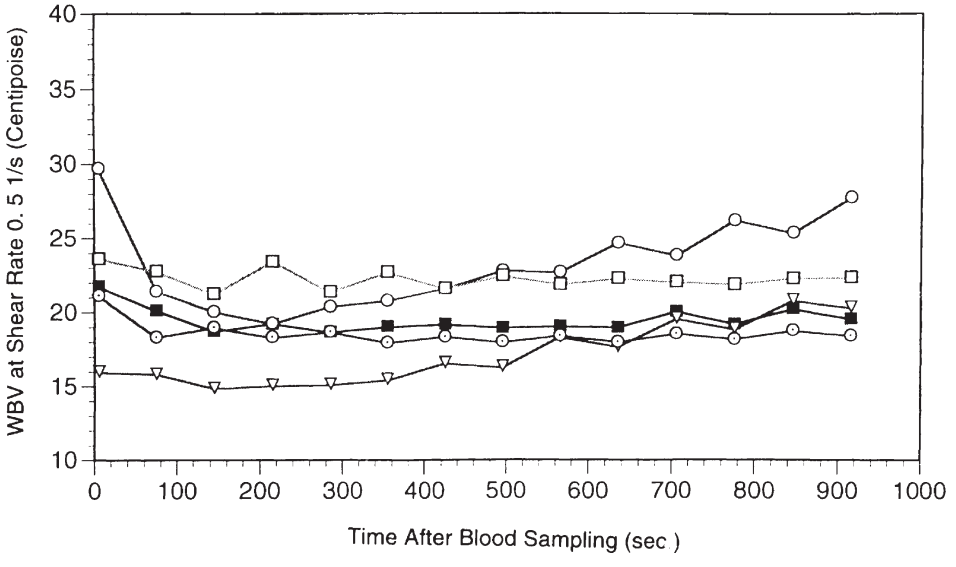
Whole-blood viscosity was measured in EDTA anticoagulated blood, the concentration of EDTA being 0.34 mol/l. All assessments were completed within 2 h. We used a Bohlin CS 10 Rheometer (Bohlin instruments Ltd, Lund, Sweden) with a 9.8 ml double-gap cell designed particularly for measuring suspensions at low shear rates. The double-gap measuring geometry involves a hollow cylinder being lowered into a cylindrical groove in the outer cylinder. The blood sample is contained in the double annular gap between them. This device was designed to take a large sample volume, making the surface of the sample as big as possible, and to optimize the accuracy at low shear rates. Since whole blood is a non-Newtonian fluid (i.e. its viscosity changes with shear rate) we performed measurements at 12 different shear rates. Each sample was stirred well immediately before measuring. We decided to discard the highest value because it was almost identical to the one at shear rate 201/s and the two below 0.5/s because the measurements became less accurate at these low shear rates. At each step there was a 60 s delay, allowing the sample to adjust to the new shear rate. The rheometer is a constant torque motor which works by a drag-cup system. An angular position sensor detects the movement of the measuring system attached to the shaft. The software automatically converts the applied value of torque to a shear stress when displaying data. The reading from the position sensor is converted to a strain. By monitoring the change of strain as a function of time, we can obtain the shear rate. The viscosity is then calculated as the shear stress : shear rate ratio.

To study the validity of our low-shear-rate data on this particular rheometer, we plotted a time versus viscosity curve at shear rate 0.5/s over 15 min. Blood samples were collected from five healthy subjects aged 35–65 years. The viscosity was stable and not altered by potentially time-dependent confounding effects such as migration of erythrocytes and sedimentation within this time range (Fig. 1).

All analyses were carried out at a temperature of 37.0°C. Each whole-blood viscosity value was assessed from the mean of data for two samples analyzed separately. The whole-blood viscosity was measured at baseline and after 60 and 120 min of clamping. The technique has an interassay coefficient of variation of less than 7% at all shear rates. Viscosity was also calculated from hematocrit level and the total plasma protein level, using the regression equations proposed by de Simone *et al.* [17].

Fasting glucose level was determined enzymatically, using a glucose dehydrogenase method and a Cobas Bio analyzer (Roche, Basel, Switzerland). We used a Reflolux II (Boehringer Mannheim GmbH, Mannheim, Germany) to measure glucose concentrations during the glucose clamp procedure. Reflolux II has previously been found to be precise, both in comparison with the Beckman Glucose Analyzer (r = 0.99) [24] and relative to the hexokinase method (within-run coefficient of variation 1.9%) [25]. In our laboratory, Reflolux rendered a correlation coefficient of r = 0.92 with the hexokinase method. Within-run variation was less than 2%.

Fig. 1



Line graph shows whole blood viscosity (WBV) at shear rate 0.5/s measured over a time scale of 15 min in five subjects. The directly measured viscosity values are stable.

Insulin was determined by radioimmunoassay [26]. Hematocrit level was determined by a laser operated ORTHO-ELT 800/WS hematology analyzer (Ortho Diagnostic Systems, Westwood, Massachusetts, USA).

Total serum protein was measured by using Cobas Integra Cassette total protein containing an in-vitro diagnostic reagent system intended for use on Cobas Integra (Roche). Blood pressure and heart rate were measured with an Omega 1000TM adult/pediatric blood pressure recorder (INVIVO Research Laboratories Inc., Tulsa, Oklahoma, USA), as previously evaluated in our laboratory [27].

Statistical analysis

The data were analyzed using the statistical package SPSS PC+ Version 3.0 (SPSS PC+ Inc., Chicago, Illinois, USA). Data are given as means ± SEM. Bivariate correlation coefficients (r) were calculated using the Pearson product moment formula or Spearman's rank test, dependent on normality of distribution or not. $P < 0.05$ (two-tailed) was considered statistically significant. Multiple regression analysis was applied to compare the relationships of whole-blood viscosity and BMI to GDR.

Results

Directly measured and calculated viscosity and hematocrit level

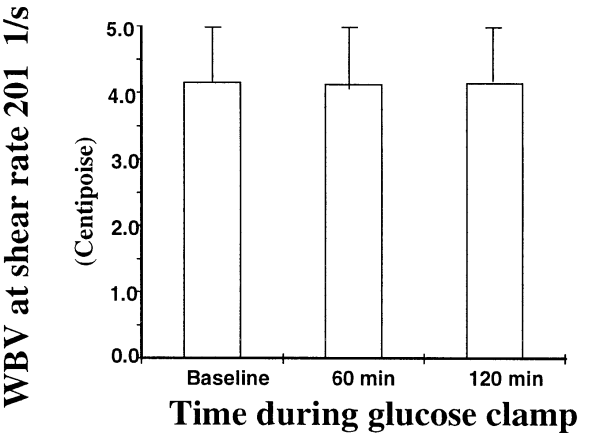
Viscosity was measured at baseline and after 1 and 2 h of glucose clamping. Whole-blood viscosity remained unchanged and was therefore not influenced by the raised plasma insulin level during clamping (Fig. 2). Hematocrit level averaged 43 ± 1% and hemoglobin level was 15.1 ± 0.2 g/l. Hematocrit level was correlated to directly measured whole-blood viscosity at shear rate 201/s (r = 0.76, $P = 0.001$) and at shear rate 0.5/s (r = 0.63, $P = 0.01$). Total plasma protein was 69 ± 1 g/l. Total plasma protein concentration was correlated positively to whole-blood viscosity (r = 0.57, $P < 0.03$).

Viscosity measured directly in whole blood was correlated to calculated blood viscosity at shear rates 201/s (r = 0.80, $P = 0.0004$), 5.8/s (r = 0.82, $P = 0.0002$), and 0.5/s (r = 0.72, $P = 0.003$). There were highly significant correlations also at intermediate shear rates.

Whole-blood viscosity and insulin sensitivity

Fasting serum glucose concentration was 5.0 ± 0.1 mmol/l and that of fasting serum insulin was 128 ± 12 pmol/l. The GDR was 6.5 ± 0.6 mg/kg body weight per min and the GDR/I averaged 8.9 ± 0.8 arbitrary units. There were statistically significant negative correlations between GDR/I and whole-blood viscosity at shear rates 2.3, 1.1 and 0.5/s (r = –0.54, $P = 0.04$). The correlation between hematocrit level and GDR/I was of borderline significance (r = 0.48, $P = 0.072$).

Fig. 2



Bar graph shows directly measured whole-blood viscosity (WBV) at shear rate 201/s assessed at baseline and after 60 and 120 min of isoglycemic glucose clamp (n = 15, 4.14 ± 0.9 cP). There was no change in whole-blood viscosity during clamping.

On expanding the material with data from 27 more subjects subsequently studied, the relationship between GDR and whole-blood viscosity became statistically highly significant both at the low shear rate of 0.5/s (r = –0.41, $P = 0.007$, n = 42) and at the high shear rate of 201/s (r = –0.41, $P = 0.007$, n = 42; Fig. 3).

Whole-blood viscosity and BMI

BMI did not correlate significantly to whole-blood viscosity either at low or at high shear rates for the original group of 15 subjects (r = 0.17, $P = 0.5$ and r = 0.18, $P = 0.5$, respectively), and for the expanded group of 42 subjects (r = 0.17, $P = 0.3$ and r = –0.07, $P = 0.7$, respectively). Seven of the 42 subjects had BMI > 27 kg/m^2. Omitting them from the analysis did not weaken the correlation between GDR and whole-blood viscosity at shear rate 201/s (r = –0.41, $P = 0.016$, n = 35).

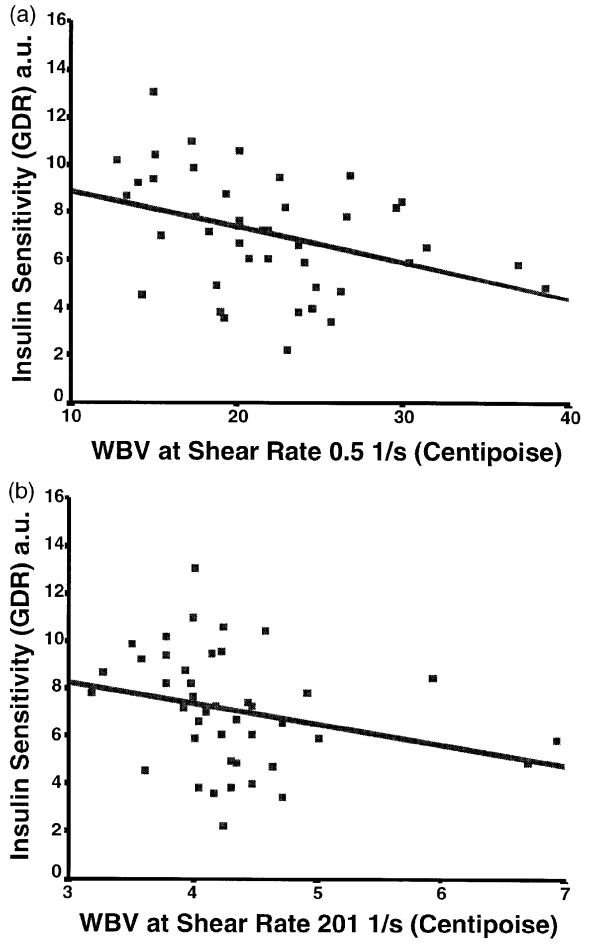
Whole-blood viscosity, insulin resistance, and BMI

We performed a multiple regression analysis (n = 42) with GDR as dependent variable and BMI and whole-blood viscosity as independent variables. Whole-blood viscosity was the only explanatory variable and explained 15% of the variation in GDR.

Whole-blood viscosity and serum lipoproteins

Serum triglyceride levels averaged 1.37 ± 0.05 mmol/l. Total cholesterol level was 4.5 ± 0.05 mmol/l and HDL cholesterol level was 0.93 ± 0.03 mmol/l. At shear rate 0.5/s whole-blood viscosity tended to be correlated negatively to HDL cholesterol level (r = –0.44, $P = 0.1$, n = 15) and was correlated positively and significantly to serum triglyceride (r = 0.51, $P = 0.04$) and total serum cholesterol (r = 0.67, $P = 0.006$) levels. At shear rate 201/s whole-blood

Fig. 3



Line graphs show negative correlations between directly measured whole-blood viscosity (WBV) at shear rates 0.5/s (a, r = –0.41, $P = 0.007$) and 201/s (b, r = –0.41, $P = 0.007$) and insulin sensitivity (glucose disposal rate, GDR). a.u., arbitrary units.

viscosity was correlated negatively to HDL cholesterol (r = –0.53, $P = 0.04$) and positively to serum triglyceride (r = 0.54, $P = 0.04$) and to total serum cholesterol (r = 0.52, $P = 0.05$; Fig. 4) levels.

Insulin sensitivity, serum lipoproteins, and BMI

GDR/I was correlated positively to serum HDL cholesterol level (r = 0.54, $P = 0.04$, n = 15). GDR/I was correlated significantly and negatively to serum triglyceride (r = –0.69, $P = 0.005$) and total serum cholesterol (r = –0.81, $P = 0.0003$) levels. There was no significant correlation between GDR and BMI either with n = 15 (r = –0.3, $P = 0.3$) or with n = 42 (r = –0.2, $P = 0.3$).

Blood pressure and heart rate

There was a positive correlation between DBP at rest and whole-blood viscosity for the shear rate of 201/s, which did not attain the level of statistical significance (r = 0.43, $P = 0.1$, n = 15). Systolic blood pressure and heart rate at rest did not correlate to whole-blood viscosity. Neither did GDR/I correlate to resting blood pressure and heart rate.

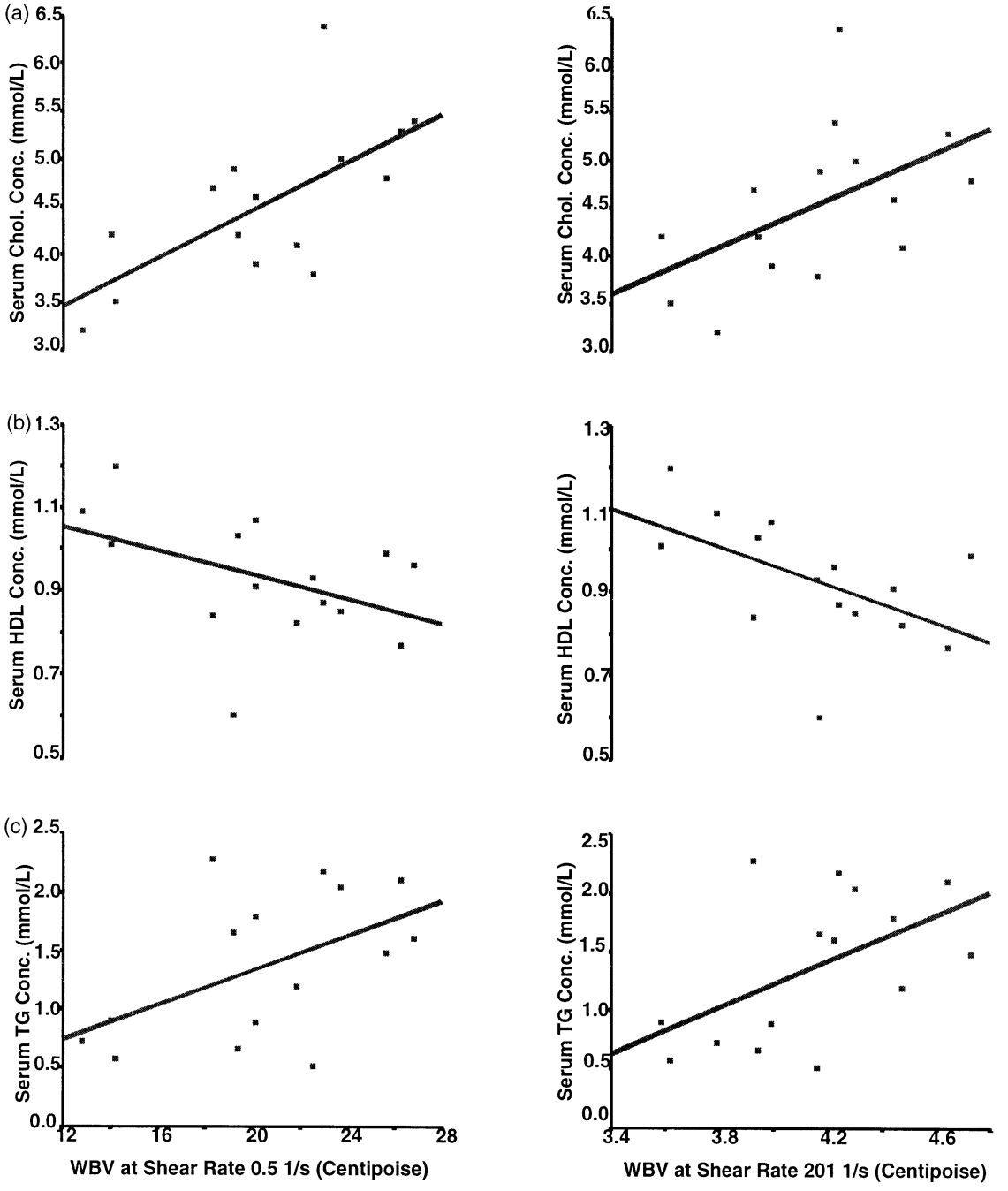
Discussion

The present results demonstrate that there is a negative relationship between directly measured whole-blood viscosity and insulin sensitivity of healthy young men. This result is in accordance with our previous observation with calculated viscosity [15,16], but it is the first time directly measured whole-blood viscosity has been related to insulin sensitivity. Insulin resistance has been linked to processes taking place both at the receptor [28] and at the postreceptor level [29]. Blood flow and the delivery of glucose to skeletal muscle have also been shown to be modulators of glucose uptake [30]. Blood flow is determined by the arterial blood pressure and by the peripheral vascular resistance, which is a function of the size and geometry of the resistance vessels, but also of blood viscosity [31]. According to the Poiseuille–Hagen law, whole-blood viscosity contributes to the total peripheral resistance. Therefore, a hemodynamic explanation for the relationship between viscosity and insulin resistance is plausible (i.e. higher whole-blood viscosity reduces the blood flow and thereby decreases delivery of glucose to skeletal muscle).

Hematocrit level is the most important single determinant of whole-blood viscosity, in that viscosity increases directly with hematocrit level throughout its normal range [14]. In addition to this, erythrocyte rigidity and aggregability determine whole-blood viscosity. Because the diameter of the erythrocytes is 8.4 μm while the smallest capillaries have a diameter of 3–5 μm, erythrocyte deformability is important in the microcirculation. A decrease in erythrocyte deformability has been attributed to alterations in the lipid composition of the cell membrane [17,22]. Higher levels of cholesterol and low-density lipoprotein may favor increased oxidation of the erythrocyte membrane lipids and lead to stiffening of the erythrocyte [17,22]. This in turn will impair flow in the microcirculation and reduce delivery of glucose to the skeletal muscle. A negative correlation of BMI to erythrocyte fluidity and a positive correlation of BMI to aggregation tendency have also been reported [32]. These factors are compatible with the hemodynamic hypothesis [6] insofar as nutritional flow and delivery of glucose to skeletal muscle are mediated through these small vessels in the microcirculation which are dependent on erythrocyte fluidity and thereby viscosity.

A reverse mechanism can also be considered. Insulin, as a growth factor, could stimulate erythropoiesis, increasing hematocrit level or stimulating the synthesis of plasma proteins. Insulin resistance has been associated with

Fig. 4



Line graphs show correlations between directly measured whole-blood viscosity (WBV) at shear rates 0.5 and 201/s and total serum cholesterol (a, $r = 0.67$, $P = 0.006$ and $r = 0.52$, $P = 0.05$), serum high-density lipoprotein (HDL) cholesterol (b, $r = -0.44$, $P = 0.1$ and $r = -0.53$, $P = 0.04$) and serum triglyceride (c, $r = 0.51$, $P = 0.04$ and $r = 0.54$, $P = 0.04$) levels.

elevated levels of insulin-like growth factor-1 [32], a substance that can stimulate erythropoiesis [33,34].

Mental stress can increase hematocrit level [35,36], and infusion of epinephrine increasing plasma epinephrine concentrations to levels that can be detected during mental stress increases hematocrit level [37] and decreases insulin-stimulated utilization of glucose [38,39]. Though blood pressure and heart rate measured during supine rest did not significantly correlate to viscosity and insulin sensitivity in the present study, possibly due to lack of statistical power or type II error, we found in a previous

study that maximal DBP during mental arithmetic stress, as opposed to resting conditions, was rather strongly negatively correlated ($r = -0.62$, $P = 0.0001$) to insulin sensitivity [40]. With the same group of young men [40], plasma adrenaline levels during mental stress were correlated positively to heart rate ($r = 0.70$) and DBP ($r = 0.53$) during stress and negatively to insulin sensitivity ($r = -0.36$). We suggested that sympathetic nervous system overactivity can be a significant modulator of the insulin-resistance syndrome [40].

In the present study we observed a rather close correlation between directly measured viscosity and viscosity calculated from the equation proposed by de Simone *et al.* [17]. They found a correlation of $0.80 \leqslant r \leqslant 0.86$, almost identical to our results. At shear rate 0.5/s the correlation was somewhat weaker ($r = 0.72$, $P = 0.003$). The reason for this is probably that variation of whole-blood viscosity will increase with lower shear rates. However, the strength of the correlation with GDR was the same at shear rates 201 and 0.5/s. The values of whole-blood viscosity at low shear rate in our study correspond well to values from other laboratories [14,20,41].

At low shear rates (i.e. below 1/s) there could be a decrease in viscosity over time [42,43], probably because of migration and sedimentation of erythrocytes. To solve this problem Bull *et al.* [44] decided to use the 'peak value' as the 'true' viscosity value. The viscosity values referred to in this work were measured after 120 s of each shear rate. We constructed a viscosity versus time plot to demonstrate that the viscosity is stable at shear rate 0.5/s with this particular rheometer, documenting that our low-shear-rate measurements are reliable.

Blood viscosity is physiologically about fourfold water's viscosity in the absence of aggregation of erythrocytes and with optimal deformation and orientation of blood cells, a condition realized at the highest shear rates, in the precapillary compartment. Blood viscosity increases progressively as shear rate decreases, and erythrocytes progressively aggregate [45]. Therefore, blood viscosity can be considered a physiologic component of peripheral resistance only at the highest shear rates, corresponding to arterioles and precapillary vessels.

Whole-blood viscosity remained unchanged during clamping. This is in accordance with our earlier observations that hematocrit level remains unchanged during clamping (unpublished data). Hyperinsulinemia can induce sodium retention [3], which can expand intravascular volume and thereby reduce viscosity. We also extract approximately 250 ml blood during clamping which we replace by saline. This would also be expected to lower the viscosity. However, sympathetic nervous system activity increases during clamping [46]. Catecholamines may increase hematocrit level [38], and possibly balance other effects that tend to lower whole-blood viscosity.

In the present study, directly measured whole blood viscosity was correlated positively and significantly to serum triglyceride and to total serum cholesterol levels and tended to be correlated negatively to HDL cholesterol levels. These results also support the hypothesis that whole-blood viscosity is a part of the insulin-resistance or metabolic cardiovascular syndrome. In parallel, insulin resistance, insulin sensitivity's inverse, exhibited the same relationships with serum triglyceride level, total serum cholesterol level and BMI and was correlated negatively to serum HDL cholesterol level in accordance with our previous findings concerning healthy young men [40]. Interestingly, Rostrup *et al.* [47] before that showed that maximal plasma catecholamine concentrations during mental stress were rather strongly related to maximal blood pressure, heart rate, serum lipoprotein levels, and BMI, which is consistent with the modulating effect of sympathetic nervous system activity. The mechanism of origin for the lipoprotein abnormalities could be hemodynamic [48].

The observed association between BMI and insulin resistance has been found for nonobese individuals [1], but is not a consistent finding [49]. Obesity is conventionally defined as a BMI greater than 27 kg/m^2; in the present study, the BMI was 25.2 ± 0.8 kg/m^2; only seven subjects had BMI exceeding 27.0 kg/m^2. Omitting their data from the analysis did not weaken the correlation between insulin sensitivity and whole-blood viscosity.

Smoking may induce insulin resistance [50,51]. Smoking increases hemoglobin concentration [52] and the hematocrit level [53], which is a possible explanation for the relationship between smoking and insulin resistance. We only had two smokers in our study, and smoking could not explain our results.

Thus, the present results demonstrate for the first time that there is a negative relationship between directly measured whole-blood viscosity and insulin sensitivity as a part of the insulin-resistance syndrome. Whole-blood viscosity contributes to the total peripheral resistance, and these results support the hypothesis that there is a hemodynamic basis for insulin resistance.

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References

1 Pollare T, Lithell H, Berne C. Insulin resistance is a characteristic feature of primary hypertension independent of obesity. *Metabolism* 1990; **39**:167–174.

2 Ferranini E, Buzzigoli G, Bonadonna R, Giorico MA, Olegqqini M, Graziadei L, *et al.* Insulin resistance in essential hypertension. *N Engl J Med* 1987; **317**:350–357.

3 DeFronzo RA. Insulin resistance: the metabolic link between non-insulin-dependent diabetes mellitus, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. *Curr Opin Cardiol* 1990; **5**:586–593.

4 Reaven GM. Insulin resistance and compensatory hyperinsulinemia: role in hypertension, dyslipidemia, and coronary heart disease. *Am Heart J* 1991; **121**:1283–1289.

5 DeFronzo RA, Gunnarsson R, Björkman O, Olsson M, Wahren J. Effects of insulin on peripheral and splanchnic glucose metabolism in noninsulin-dependent (type II) diabetes mellitus. *J Clin Invest* 1985; **76**:149–155.

6 Julius S, Gudbrandsson T, Jamerson K, Tariq Shabab S, Andersson O. The hemodynamic link between insulin resistance and hypertension. *J Hypertens* 1991; **9**:983–986.

7 Laakso M, Edelman V, Brechtel G, Baron AD. Decreased effect of insulin to stimulate skeletal muscle blood flow in obese man. *J Clin Invest* 1990; **85**:1844–1852.

8 Baron AD, Laakso M, Brechtel G, Hoit B, Watt L, Edelmann SV. Reduced postprandial skeletal muscle blood flow contributes to glucose intolerance in human obesity. *J Clin Endocrinol Metab* 1990; **79**:1525–1533.

9 Lillioja S, Young A, Culter C, Ivy JL, Abbott WG, Zawadzki JK, *et al.* Skeletal muscle capillary density and fiber type are possible determinants of *in vivo* insulin resistance in man. *J Clin Invest* 1987; **80**:415–424.

10 Lowe GD, Drummond MD, Lorimer AR, Hutton I, Forbes CD, Prentice CR, *et al.* Relation between extent of coronary artery disease and blood viscosity. *BMJ* 1980; **2**:673–674.

11 Raier C, Kawanashi DT, Chandraratna AN. Changes in blood rheology in patients with stable angina pectoris as a result of coronary artery disease. *Circulation* 1987; **76**:15–20.

12 Devereux RB, Drayer JIM, Chien S, Pickering TG, Letcher RL, DeYoung JL, *et al.* Whole blood viscosity as a determinant of cardiac hypertrophy in systemic hypertension. *Am J Cardiol* 1984; **54**:592–595.

13 Dormandy JA, Hoare A, Colley J, Arrowsmith DE, Dormandy TL, *et al.* Clinical, haemodynamic, rheological, and biochemical findings in 126 patients with intermittent claudication. *BMJ* 1973; **4**:576–581.

14 Letcher RL, Chien S, Pickering T, Sealey JE, Laragh JH. Direct relationship between blood pressure and blood viscosity in normal and hypertensive subjects. *Am J Med* 1981; **70**:1195–1202.

15 Moan A, Nordby G, Os I, Birkeland KI, Kjeldsen SE. Relationship between hemorheologic factors and insulin sensitivity in healthy young men. *Metabolism* 1994; **43**:423–427.

16 Nordby G, Moan A, Kjeldsen SE, Os I. Relationship between hemorheological factors and insulin sensitivity in normotensive and hypertensive premenopausal women. *Am J Hypertens* 1995; **8**:439–449.

17 de Simone G, Devereux RB, Chien S, Alderman MH, Atlas SA, Laragh JH. Relation of blood viscosity to demographic and physiologic variables and to cardiovascular risk factors in apparently normal adults. *Circulation* 1990; **81**:107–117.

18 Lithell H. Hypertension and hyperlipidemia. *Am J Hypertens* 1993; **6**:303S–308S.

19 Koenig W, Sund M, Ernst E, Mraz W, Hombach V, Keil U. Association between rheology and components of lipoproteins in human blood. Results from the Monica project. *Circulation* 1992; **85**:2197–2204.

20 Letcher RL, Shu Chien, Pickering TG. Elevated blood viscosity in patients with borderline essential hypertension. *Hypertension* 1983; **5**:757–762.

21 Lowe GD. Blood viscosity and cardiovascular risk. *Curr Opin Lipidol* 1993; **4**:283–287.

22 Crowley JP, Metzger BS, Assaf A. Low density lipoprotein cholesterol and whole blood viscosity. *Ann Clin Lab Sci* 1994; **24**:533–541.

23 DeFronzo R, Tobin J, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979; **237**:E214–E223.

24 Thai AC, Ng WY, Lui KF, Yeo PP. Three new glucose reflectance meters: Diascan, Glucometer II and Reflolux II. *Diabetes Res Clin Pract* 1989; **7**:75–81.

25 Regal H, Zdolsek I, Irsigler K. Comparison of the accuracy and precision of seven reflectometers in self-control of blood glucose. *Wien Med Wochenschr* 1989; **139**:56–61.

26 Følling I, Norman H. Hyperglycemia, hypoglycemic attacks and production of anti-insulin antibodies without previous known immunization. Immunological and functional studies in patients. *Diabetes* 1972; **21**:814–826.

27 Rostrup M, Kjeldsen SE, Eide I. Awareness of hypertension increases blood pressure and sympathetic responses to cold pressor test. *Am J Hypertens* 1990; **3**:912–917.

28 Kahn CR. Role of insulin receptors in insulin resistant states. *Metabolism* 1980; **29**:455–466.

29 Crettaz M, Jeanraud B. Postreceptor alterations in the states of insulin resistance. *Metabolism* 1980; **29**:467–477.

30 Schultz TA, Lewis BL, Westbie DK. Glucose delivery: a modulator of glucose uptake in contracting skeletal muscle. *Am J Physiol* 1977; **233**:E514–E518.

31 Stuart J, Kenny MW. Blood rheology. *J Clin Pathol* 1980; **33**:417–429.

32 Linde T, Sandhagen B, Hagg A. Blood viscosity and peripheral vascular resistance in patients with untreated essential hypertension. *J Hypertens* 1993; **11**:731–736.

33 Urena P, Bonnadreaux A, Eckardt KU, Kurtz A, Drueke TB. Insulin-like growth factor I: a modulator of erythropoiesis in uraemic patients? *Nephrol Dial Transplant* 1992; **7**:40–44.

34 Kurtz A, Zapf J, Eckardt KU, Clemons G, Froesch ER, Bauer C. Insulin-like growth factor I stimulates erythropoiesis in hypophysectomized rats. *Proc Natl Acad Sci USA* 1988; **85**:7825–7829.

35 Burch GE, DePasquale NP. The hematocrit in patients with myocardial infarction. *JAMA* 1963; **180**:143–145.

36 Jern C, Wadenvik H, Mark H, Hallgren J, Jern S. Hematological changes during acute mental stress. *Br J Haematol* 1989; 71:153–156.

37 Kjeldsen SE, Weder AB, Egan B, Neubig R, Zweifler AJ, Julius S. Effect of circulating adrenaline on platelet function and hematocrit. *Hypertension* 1995; **25**:1096–1105.

38 Hamburg S, Hendler R, Sherwin RS. Influence of small increments of adrenaline on glucose tolerance in normal humans. *Ann Int Med* 1980; **93**:566–568.

39 Sherwin RS, Shamoon H, Hendler R, Sacca L, Eigler N, Walesky M. Adrenaline and the regulation of glucose metabolism: effect of diabetes and hormonal interactions. *Metabolism* 1980; **29 (suppl 1)**:1146–1154.

40 Moan A, Nordby G, Rostrup M, Eide I, Kjeldsen SE. Insulin sensitivity, sympathetic activity, and cardiovascular reactivity in young men. *Am J Hypertens* 1995; **8**:268–275.

41 Zannad F, Stoltz J-F. Blood rheology in arterial hypertension. *J Hypertens* 1992; **10**:569–578.

42 Cokelet GR, Smith JH. The effect of concentric-cylinder viscometer gap size on the experimental rheological properties of human blood. *Biorheology* 1972; **10**:51–56.

43 Chien S, Usami S, Taylor HM, Lundberg JL, Gregersen MI. Effect of hematocrit and plasma proteins on human blood rheology at low shear rates. *J Appl Physiol* 1966; **21**:81–87.

44 Bull BS, Chien S, Dormandy JA, Kiesewetter H, Lewis SM, Lowe DO, *et al.* International Committee for Standardization in Haematology. Guidelines for measurement of blood viscosity and erythrocyte deformability. *Clin Hemorheol* 1986; **6**:439–453.

45 Chien S. Shear dependence of effective cell volume as a determinant of blood viscosity. *Science* 1970; **168**:977–979

46 Moan A, Høieggen A, Nordby G, Birkeland K, Eide I, Kjeldsen SE. The glucose clamp procedure activates the sympathetic nervous system even in the absence of hyperinsulinemia. *J Clin Endocrinol Metabol* 1995; **80**:3151–3154.

47 Rostrup M, Westheim A, Kjeldsen SE, Eide I. Cardiovascular reactivity, coronary risk factors, and sympathetic activity in young men. *Hypertension* 1993; **22**:891–899.

48 Dzau VJ, Sacks FM. Regulation of lipoprotein metabolism by adrenergic mechanisms. *J Cardiovasc Pharmacol* 1987; **10 (suppl 9)**:S2–S6.

49 Caro JF. Insulin resistance in obese and nonobese man. *Clin Endocrinol Metab* 1991; **73**:691–696.

50 Facchini FS, Hollenbeck CB, Jeppesen J, Chen YD, Reaven GM. Insulin resistance and cigarette smoking. *Lancet* 1992; **339**:1128–1130.

51 Attvall S, Fowelin J, Lager I, Von Schenk H, Smith U. Smoking induces insulin resistance – a potential link with the insulin resistance syndrome. *J Intern Med* 1993; **233**:327–332.

52 Nordenberg D, Yip R, Binkin JR. The effect of cigarette smoking on hemoglobin levels and anemia screening. *JAMA* 1990; **264**:1556–1559.

53 Yarnell JW, Sweetnam PM, Rogers S, Elwood PC, Bainton D, Baker IA. Some long term effects of smoking on the haemostatic system: a report from the Caerphilly and Speedwell Collaborative Surveys. *J Clin Pathol* 1987; **40**:909–913.