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Blood Viscosity, Plasma Adrenaline and Fasting Insulin in Hypertensive Patients with Left Ventricular Hypertrophy

ICARUS, a LIFE Substudy

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We have seen relationships between whole blood viscosity (WBV) and components of the metabolic cardiovascular syndrome in borderline hypertensive young men and suggested that sympathetic nervous system (SNS) activity may be a mediator. In the present study we aimed to test this hypothesis in established hypertension and to investigate the relationship between WBV and cardiac dimensions. Unmedicated patients ($n = 42$) with stage II–III hypertension and electrocardiographic left ventricular hypertrophy (LVH) underwent hyperinsulinemic isoglycemic glucose clamp to assess glucose disposal rate (GDR) and echocardiographic studies. WBV, plasma catecholamines and insulin were measured in arterialized venous blood. WBV at high shear rate correlated with baseline plasma adrenaline ($r = 0.33$, $p = 0.04$) and fasting insulin ($r = 0.34$, $p = 0.04$) while there was a negative trend for GDR ($r = -0.21$, $p = 0.2$). WBV at low shear rate correlated with plasma adrenaline ($r = 0.49$, $p = 0.002$) and resting heart rate ($r = 0.36$, $p = 0.02$). WBV was higher in smokers than in non-smokers ($p = 0.02$) and in males than in females ($p = 0.02$). Fasting insulin independently explained 12% of the variation in WBV at high shear, while baseline adrenaline independently explained 17% of the variation in WBV at low shear. Systolic blood pressure explained 31% of the variation in LV mass index. Thus, we demonstrate positive relationships between blood viscosity versus plasma adrenaline and fasting insulin in hypertensive patients with LVH. We suggest that adrenergic activity may increase hematocrit and viscosity and hence reduce insulin sensitivity. *Key words: hypertension, insulin resistance, plasma adrenaline, sympathetic nervous system activity, whole blood viscosity.*

INTRODUCTION

Whole blood viscosity (WBV) has been suggested to be an independent risk factor for cardiovascular disease [1–3] and peripheral vascular disease [4], and it is a correlate of both systolic and diastolic blood pressure [5]. Devereux *et al*. [3] reported that left ventricular mass (LVM) was more closely related to WBV than to blood pressure in hypertensive patients, and Lowe *et al*. [6] recently showed that WBV was as strong a predictor of cardiovascular events as cholesterol and diastolic blood pressure, and stronger than smoking, in the elderly. In prior studies we showed that *calculated* WBV was negatively related to insulin sensitivity both in borderline hypertensive young men [7] and in mildly hypertensive premenopausal women [8]. Recently we also demonstrated a negative association between *directly measured* WBV and insulin sensitivity in groups of borderline hypertensive young men [9, 10]. Hematocrit is the most important single determinant of WBV at any shear rate, and is also independently related to insulin resistance in healthy non-obese subjects [11]. WBV increases linearly with hematocrit throughout its normal range [5]. Hematocrit increases during adrenaline infusion [12] and during mental stress [13, 14]. Cathecolamines may induce hemoconcentration acutely by increased peripheral capillary filtration due to venoconstriction [15]. Increased adrenergic activity may therefore contribute to increased WBV which again is a determinant of peripheral resistance according to the Poiseuille–Hagen equation.

Left ventricular hypertrophy (LVH) is related to blood pressure [3], but also to sympathetic nervous system (SNS) activity [16] and WBV [3]. Hyperinsulinemia as a consequence of insulin resistance, may promote vascular

Table I. *Inclusion and exclusion criteria*

Inclusion criteria
1. Essential hypertension with a systolic blood pressure between 160 and 200 mmHg and/or a diastolic blood pressure between 95 and 115 mmHg
2. Left ventricular hypertrophy assessed by electrocardiography in accordance to the Cornell voltage–duration criteria: (RaVL + SV3 mm + (6 mm (for women)) × QRS-duration >2.440 mm × ms or the Sokolov–Lyon criteria: SV1 + RV5 or RV6 > 38 mm
3. Age between 55 and 80 years
Exclusion criteria
1. Angina pectoris demanding treatment with beta- or calcium-receptor antagonists
2. Chronic heart failure demanding medication at time of inclusion
3. Aortic stenosis (Doppler gradient >20 mmHg)
4. Serum creatinine >0.160 mmol/l
5. Valvular heart disease
6. Severe obstructive pulmonary disease
7. Myocardial infarction or stroke within 6 months

and cardiac growth [17, 18] as well as contribute to higher WBV by stimulating hematopoiesis [19]. In the present study we aimed to test the hypothesis that WBV may be related to sympathoadrenergic activity and insulin resistance in patients with long-standing hypertension and LVH, and to investigate the relationship between WBV and cardiac dimensions in these subjects.

SUBJECTS AND METHODS

Subjects

In the "Insulin CARotids US Scandinavia" (ICARUS) Study we measured WBV in 39 of 42 patients investigated at Ullevaal University Hospital, Oslo, Norway. There were 31 men and 11 women with essential hypertension and LVH as determined by electrocardiogram (ECG), median age 69 (7) years, after two weeks of placebo treatment. All patients were included in the clinical trial "Losartan Intervention For Endpoint (LIFE) reduction in hypertension" [20] and met the inclusion and exclusion criteria (Table I). The ICARUS Study group consists of investigators from Denmark (Department of Internal Medicine, Glostrup Hospital, University of Copenhagen), USA (Department of Internal Medicine, University of Michigan Medical Center, The Clinical Research group of Oregon, Oregon and The Mount Sinai Medical Center, New York) and Norway (Department of Cardiology, Ullevaal Hospital, University of Oslo). There were eight smokers and 34 non-smokers. Baseline clinical and metabolic characteristics are listed in Table II, with the values for men and women given separately.

Blood pressure measurements

According to the protocol of the LIFE study [20] sitting blood pressure was measured at the time of randomization using a manual mercury sphygmomanometer. Furthermore, in connection with the isoglycemic clamp, blood pressure and heart rate were measured with an Omega 1000TM Adult/Pediatric Blood Pressure Recorder (IN-VIVO Research Laboratories Inc., Tulsa, OK, USA), as previously evaluated in our laboratory [21].

Glucose clamp examination. An antecubital vein on the right arm was cannulated with a short teflon catheter (Venflon® 17G, Viggo AB, Helsingborg, Sweden) and the right forearm was then placed in a heating sleeve (Thermal Vascular Dilatator, Swetron AB, Veddesta, Sweden). The temperature in the heating device was set at 52.0°C, and the right arm was thus used for sampling arterialized venous blood. This approach allows the best estimation of arterial blood glucose. 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 30 min before recording 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.* [22] as previously detailed [7, 23]. Insulin was infused at a fixed rate of 50 mU/m^2/min. Blood glucose was clamped at the subjects fasting level (isoglycemia); this was obtained by measuring glucose concentration every 5 min (Accutrend, Mannheim Boehringer GmbH, Mannheim, Germany) and adjusting the rate of an intravenous (i.v.) infusion of glucose (200 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. This technique for measuring GDR has a day-to-day coefficient of variation (CV) of 5% in our laboratory [7, 23].

Analytical methods. WBV was measured in EDTA-anticoagulated blood using a Bohlin CS 10 rotational double-gap Rheometer (Bohlin Instruments Ltd, Lund,

Table II. *Characteristics of the study population*

	Women ($n = 11$)	Men ($n = 31$)	p-value
Age (years)[a]	69 (7)	69 (7)	n.s.
Body mass index (kg/m^2)	27 ± 2	26 ± 0.5	n.s.
Glucose (mmol/l)[a]	5.1 (0.8)	5.2 (0.5)	n.s.
Insulin (pmol/l)	138 ± 7	128 ± 6	n.s.
Glucose disposal rate (mg/kg/min)	7.5 ± 0.7	5.6 ± 0.2	n.s.
Supine systolic blood pressure (mm Hg)	175 ± 7	172 ± 4	n.s.
Supine diastolic blood pressure (mm Hg)	92 ± 4	97 ± 3	n.s.
Supine heart rate (beats/min)	66 ± 2	65 ± 2	n.s.
Hematocrit (fraction)[a]	0.40 (0.03)	0.43 (0.03)	0.03
Hemoglobin (g/100ml)[a]	12.9 (1.1)	13.9 (1.2)	0.04
Fibrinogen (g/l)[a]	2.6 (0.6)	2.9 (0.7)	n.s.
Total cholesterol (mmol/l)	6.0 ± 0.3	5.6 ± 0.2	n.s.
High density lipoprotein (mmol/l)	1.8 ± 0.1	1.4 ± 0.1	n.s.
Triglycerides (mmol/l)	1.0 ± 0.1	1.2 ± 0.1	n.s.

Mean $\pm$ SE; [a]Median and interquartile range; n.s. = not significant.

Sweden) as previously detailed [9]. Measurements were performed at low (0.5 and 1.1 s^{-1}) and high (99 and 201 s^{-1}) shear rates at a temperature of 37°C. The technique has an interassay CV of less than 7% at all shear rates.

Fasting glucose was determined enzymatically, using a glucose dehydrogenase method and a Cobas Bioanalyzer (Roche, Basel, Switzerland). Plasma catecholamines were measured by the radioenzymatic method of Peuler & Johnson [24] as previously reported [25]. Insulin was determined by radioimmunoassay [26]. Hematocrit was determined by a laser-operated ORTHO-ELT 800/WS hematology analyzer (Ortho Diagnostic Systems, Westwood, MA, USA).

Echocardiography

Echocardiographic measurements were performed with a Vingmed CFM-750 (Vingmed, Horten, Norway) in 33 patients. These measurements have day-to-day CV of 7–10% in our laboratory. The thickness of the interventricular septum (IVST) and left ventricular posterior wall (PWT) and the left ventricular internal diameter (LVID) were measured at end-diastole according to recommendations from the American Society of Echocardiography. Studies were performed and measurements made using procedures adapted from those applied in previous multicenter studies [27–29]; all measurements were verified by an experienced physician-investigator. LVM was calculated with the equation [30] $LVM = 1.04[(IVST + LVID + PWT)^3 - LVID]^3 + 0.6$ g. Left ventricular mass index (LVMI) was calculated as LVM/body surface area.

Statistical analysis

The data were analysed using the statistical package SPSS Version 8.0 (SPSS Inc., Chicago, IL, USA). The distributions of data were tested for normality by Kolmogorov–Smirnov's test. Logarithmic transformations were performed when it improved the normality distribution. Data are presented as mean $\pm$ standard error of the mean (SEM) or median (interquartile range). Differences were tested by unpaired two-tailed Student's t-test or Mann–Whitney test depending on normal distribution. For correlation analysis the Pearson product moment formula (r) or Spearman's rank test ($\rho = r'$) was used. Two-tailed $p < 0.05$ was considered the limit of statistical significance. Stepwise multiple regression analysis was applied to determine independent explanatory variables of WBV and LVMI.

RESULTS

Whole blood viscosity

Low-shear WBV (0.5 and 1.1 s^{-1}) correlated with baseline adrenaline ($r' = 0.49$, $p = 0.002$, $r' = 0.50$, $p = 0.001$; Fig. 1), plasma adrenaline at 60 min ($r' = 0.32$, $p = 0.05$) and 120 min of clamp ($r' = 0.33$, $p = 0.04$) and supine heart rate before clamp ($r' = 0.36$, $p = 0.02$, both shear rates; Fig. 2). High shear WBV (99 and 201 s^{-1}) correlated with baseline adrenaline ($r' = 0.33$, $p = 0.04$, $r' = 0.31$, $p = 0.06$; Fig. 1), fasting insulin ($r = 0.34$, $p = 0.04$, both shear rates; Fig. 2), body mass index (BMI) ($r = 0.34$, $p = 0.04$, $r = 0.31$, $p = 0.05$) and tended to correlate inversely with GDR ($r' = -0.21$, $p = 0.2$). There was no significant relationship between WBV at any shear rate and plasma noradrenaline ($r = 0.03$–0.20), age, blood pressures or serum lipids.

There were positive correlations between WBV at low

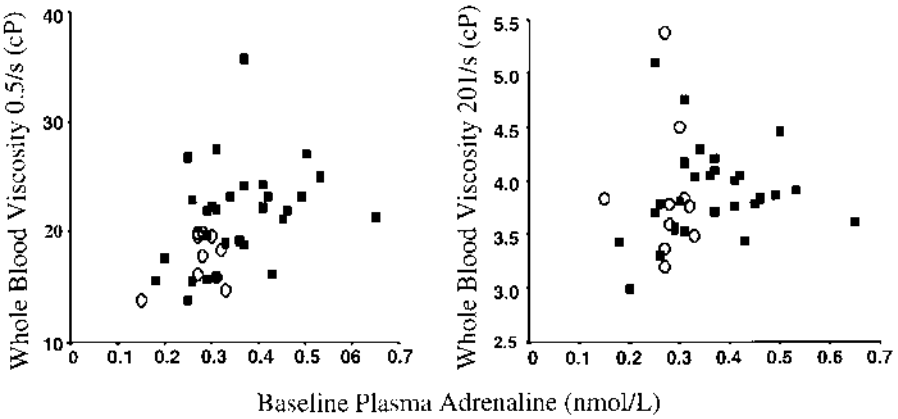

Fig. 1. Scatterplots showing the relationship between whole blood viscosity (WBV) and baseline adrenaline concentration at low (0.5 s^{-1}) shear rate ($r' = 0.49$, $p = 0.002$) (left) and high (201 s^{-1}) shear rate ($r' = 0.31$, $p = 0.06$) (right). ○ = women, ■ = men.

shear rates and baseline adrenaline ($r' = 0.41$, $p = 0.03$, $r' = 0.44$, $p = 0.02$) and a trend at high shear rates ($r = 0.35$, $p = 0.06$, $r = 0.32$, $p = 0.09$) *in men* ($n = 31$) when analysed separately. Ln WBV 99 and 201 s^{-1} correlated with fasting insulin ($r = 0.50$, $p = 0.006$, $r = 0.47$, $p = 0.01$), while a negative trend was observed with GDR ($r = -0.21$ and -0.23, n.s.). *In women* ($n = 11$) there was no significant correlation between any of these parameters.

Hematocrit correlated with WBV at low ($r' = 0.63$, $p < 0.001$) and high shear rates ($r' = 0.36$, $p = 0.02$), with baseline adrenaline ($r' = 0.31$, $p = 0.04$) and with supine HR ($r' = 0.31$, $p = 0.04$). Hematocrit and hemoglobin were higher in men than in women (Table II).

Effects of gender and smoking on whole blood viscosity and plasma adrenaline. WBV 0.5 s^{-1} averaged 17.6 ± 0.8 versus 21.4 ± 0.9 centipoise (cP) in women and men, respectively ($p = 0.02$; Fig. 3) and 3.9 ± 0.2 versus 3.9 ± 0.1 cP, respectively, at shear rate 201 s^{-1} ($p = 0.9$). WBV 0.5 s^{-1} was 23.8 ± 1.1 in smokers versus 19.8 ± 0.8 cP in non-smokers ($p = 0.02$; Fig. 3) and 4.10 ± 0.13 versus 3.82 ± 0.08 cP ($p = 0.1$), respectively, at high shear rate.

Baseline plasma adrenaline was significantly lower in women (0.280 (0.050) nmol/l) than in men (0.340 (0.140) nmol/l, $p = 0.04$), but did not differ between smokers and non-smokers ($p = 0.1$). BMI was similar between genders ($p = 0.6$) and there was no correlation between BMI and baseline adrenaline ($r' = -0.18$, $p = 0.5$).

Echocardiographic results. LVM and LVID in diastole were higher in men than in women (Table III), while LVMI, IVST, PWT and relative wall thickness

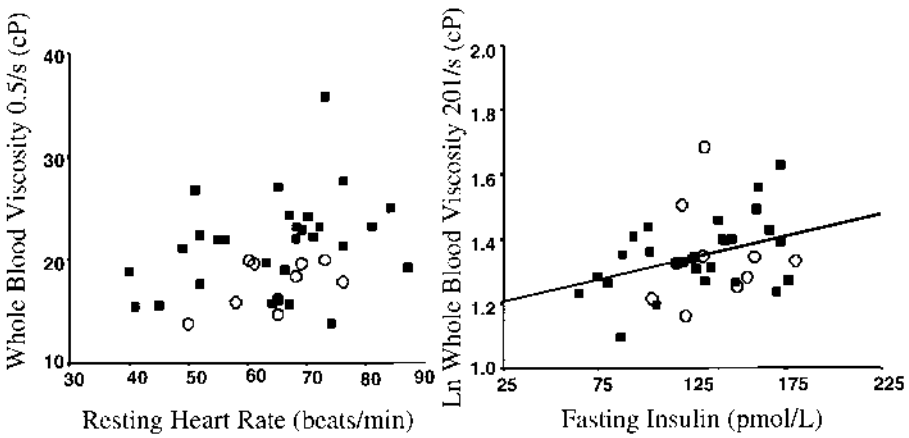

Fig. 2. Scatterplots showing the relationship between whole blood viscosity (WBV) and resting supine heart rate at low (0.5 s^{-1}) shear rate ($r' = 0.36$, $p = 0.02$) (left) and with fasting insulin at high (201 s^{-1}) shear rate ($r = 0.34$, $p = 0.04$) (right). ○ = women, ■ = men.

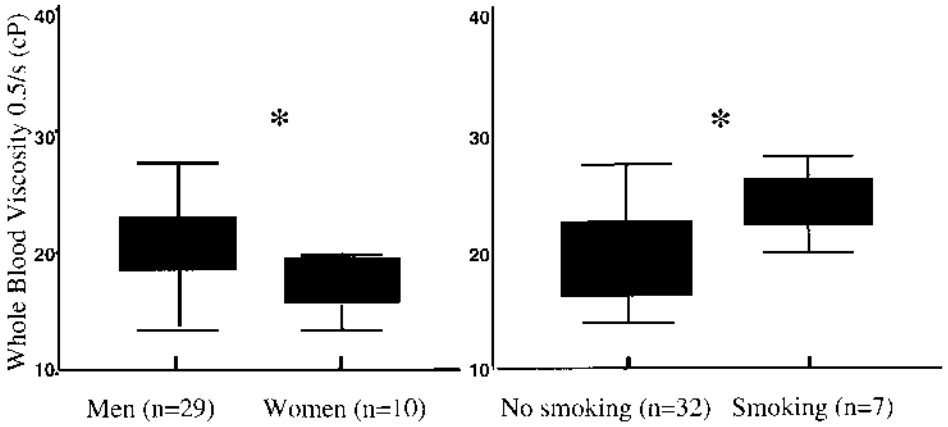

Fig. 3. Boxplots showing WBV at shear rate 0.5 s^{-1} in men and women (left),* = $p = 0.02$ and in non-smokers and smokers (right), * = $p = 0.02$.

(RWT) were similar in the two genders. Supine systolic blood pressure in the laboratory before clamp correlated significantly with LVM ($r = 0.48$, $p = 0.005$), LVID ($r = 0.40$, $p = 0.02$) and LVMI ($r = 0.56$, $p = 0.001$). Fasting insulin tended to correlate with PWT ($r = 0.25$, n.s.) and RWT ($r = 0.32$, n.s.). No statistically significant correlation between cardiac dimensions and WBV, nor between cardiac dimensions and baseline adrenaline was found.

Multivariate analysis. We used a stepwise multiple regression analysis with WBV 201 s^{-1} as a dependent variable and baseline adrenaline, gender, smoking, BMI, heart rate and fasting insulin as independent variables. Fasting insulin independently explained 12% of the variation in WBV. Logarithmic transformation of the variables did not influence this result. In a similar analysis with WBV 0.5 s^{-1} as dependent and baseline adrenaline, gender, smoking, BMI, heart rate and fasting insulin as independent variables, baseline adrenaline explained 17% of the variation in WBV. Logarithmic transformation of all variables in the analysis increased the level of explanation to 22%. Supine systolic blood pressure explained 31% of the variation in LVMI in analysis with age, gender, BMI and supine systolic blood pressure as independent variables.

DISCUSSION

Whole blood viscosity and sympathetic activity

We demonstrate positive correlations between WBV, plasma adrenaline and resting heart rate in subjects with long-standing hypertension and ECG-LVH. Mental stress, as well as adrenaline infusion to plasma levels corresponding to those seen during mental stress, increase the hematocrit [12, 13, 31]. There is hardly any evidence that erythrocyte mass is increasing during mental stress in humans [13]. Hemoconcentration, which may be the result of increased peripheral capillary filtration due to alpha-receptor mediated venoconstriction induced by adrenergic activity [15], may be a more likely explanation. Increased hematocrit and WBV have been demonstrated during a 20-min frustrating cognitive task [14] and after an 80-min exciting videofilm performance [32]. Few studies of natural stresses and long-term effects of stress

Table III. *Left ventricular structure*

	Women ($n = 8$)	Men ($n = 25$)	*p*-value
Left ventricular mass (g)	206 ± 9	252 ± 8	0.006
Left ventricular mass index (g/m^2)	121 ± 5	128 ± 4	n.s.
Inter ventricular septal thickness (cm)	1.2 ± 0.05	1.1 ± 0.04	n.s.
Left ventricular internal diameter (cm)	5.0 ± 0.1	5.5 ± 0.1	0.02
Posterior wall thickness (cm)	1.0 ± 0.03	1.1 ± 0.02	n.s.
Relative wall thickness (fraction)	0.42 ± 0.02	0.41 ± 0.01	n.s.

Mean $\pm$ SE; n.s. = not significant.

on hemorheology have been performed. We are aware of one Japanese study in 42 hypertensive subjects, however, showing elevated blood pressures, hematocrit and fibrinogen for weeks after a major earthquake [33].

Plasma adrenaline concentration is frequently used to assess SNS activity. Venous samples may not equal arterial ones because of variation in tissue uptake. In the present study we did not detect a similar relation between noradrenaline and WBV as with adrenaline. One explanation may be that venous noradrenaline originates from different organs with different sympathetic activity. The positive relations between WBV/hematocrit and heart rate support our finding, since heart rate also may be considered a simple and indirect measure of sympathoadrenergic activity.

Whole blood viscosity and insulin resistance. We observed a positive relationship between WBV and fasting insulin as well as a negative trend with GDR. This extends to patients with long-standing hypertension our previous observations in young borderline [7, 9, 10] and mildly hypertensives [8]. Insulin resistance has been linked to processes taking place both at the receptor [34] and the post-receptor level [35]. Blood flow and the glucose delivery to skeletal muscle have also been shown to be modulators of glucose uptake [36]. Blood flow is mainly determined by the peripheral vascular resistance, which is a function of the size of the resistance vessels, but also of blood viscosity [37]. The influence of WBV may be greater in a compromised circulation than in a normal one, but reduced blood viscosity was responsible for 50% of the increase in cerebral blood flow after hemodilution in healthy subjects [38]. A correlation between WBV and peripheral resistance has been demonstrated in hypertensives [39]. Therefore, one possible explanation for the relationship between viscosity and insulin resistance may be hemodynamic. A reverse mechanism can also be considered; insulin as a growth factor, could stimulate erythropoiesis [19], thus increasing the hematocrit level or the synthesis of plasma proteins.

While high shear WBV represents the flow conditions in most parts of the vascular bed, low shear WBV is typical in areas with low flow of different reasons and is considered to be a measure of red cell aggregation [40, 41]. Thus, we observed correlations between insulin and WBV at high, but not at low shear rate. High shear viscosity may be closer related to nutritional flow and thereby to insulin sensitivity.

Whole blood viscosity and left ventricular hypertrophy. We were not able to detect a relationship between WBV and LV structure, in constrast to other studies [3, 42]. Since all our subjects had LVH on qualifying ECG, we may lack the scatter necessary to detect an association between WBV and cardiac dimensions. Our subjects also differ in several ways from patients in other studies. They are survivors of long-standing hypertension without significant ischemic heart disease, but with LVH on ECG. Components of the metabolic cardiovascular syndrome are not as expressed as expected in these subjects [43]. Possibly, subjects with metabolic syndrome and high levels of WBV are already affected by coronary heart disease and therefore excluded from this study. This is also reflected in the relatively low levels of WBV in the group as a whole, being lower than in healthy blood donors [44]. Even though the present study was performed after 2 weeks of placebo wash-out, prior antihypertensive therapy may have influenced on the results. Systolic blood pressure, on the other hand, explained 31% of the variation in LVMI. Systolic blood pressure also correlated with minimal forearm vascular resistance in men from the same population [43].

Whole blood viscosity, gender and smoking. WBV was significantly lower in women than in men at low shear rates. Gender difference in WBV is a frequent finding [42, 44] and probably reflects the lower hematocrit values in women which is also present here. We have not studied gender differences in detail as there are many fewer women than men. However, the relationship between WBV, plasma adrenaline and fasting insulin seems to be less expressed in the women.

Smoking increases hemoglobin concentration [45] and the hematocrit level [46], which is a possible explanation for the relationship between smoking and WBV (and even smoking and insulin resistance). The eight smokers in the present study had higher WBV than the non-smokers. Less smoking may also partly explain the lower WBV values in the present study compared to healthy blood donors [44]. There were 32% smokers among the blood donors, compared to only 19% (8/42) in the present group.

In conclusion, blood viscosity is associated with plasma adrenaline and fasting insulin in subjects with long-standing hypertension and ECG-LVH. Increased adrenergic activity may raise hematocrit, viscosity and hence reduce insulin sensitivity.

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