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Blood viscosity and risk of cardiovascular events: the Edinburgh Artery Study

G. D. O. Lowe,[1] A. J. Lee,[2] A. Rumley,[1] J. F. Price[2] and F. G. R. Fowkes[2] [1]*Department of Medicine, University of Glasgow, Royal Infirmary, Glasgow, and* [2]*Wolfson Unit for the Prevention of Peripheral Vascular Diseases, Department of Public Health Sciences, University of Edinburgh, Edinburgh*

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Summary. We examined the relationships of whole blood viscosity and its major determinants to incident cardiovascular events (ischaemic heart disease and stroke) in a prospective study of a random population sample of 1592 men and women aged 55–74 years (the Edinburgh Artery Study). 272 fatal and non-fatal cardiovascular events occurred during 5 years of follow-up (cumulative incidence 17·1%). Age and sex adjusted mean levels of blood viscosity (3·70 *v* 3·55 mPa.s), haematocrit (46·2 *v* 45·7%), haematocrit-corrected blood viscosity (3·57 *v* 3·48 mPa.s), plasma viscosity (1·35 *v* 1·33 mPa.s) and fibrinogen (2·88 *v* 2·67 g/l) were significantly higher in subjects who experienced events than in subjects who did not. The relationships of these rheological variables to cardiovascular events were at least as strong as those of conventional risk factors (smoking habit, diastolic blood pressure, and low-density lipoprotein cholesterol). After adjustment for these conventional risk factors, the associations of blood viscosity and haematocrit remained significant for stroke, but not for total events; whereas the associations of plasma viscosity and fibrinogen remained significant for total events and for stroke.

These findings suggest that increased blood viscosity may be one plausible biological mechanism through which increases in haematocrit and fibrinogen may promote ischaemic heart disease and stroke. Randomized controlled trials of viscosity reduction in the prevention of cardiovascular events (e.g. by lowering high levels of haematocrit or plasma fibrinogen) are suggested.

Keywords: blood viscosity, haematocrit, fibrinogen, stroke, ischaemic heart disease.

Blood viscosity is the intrinsic resistance of blood to flow in vessels. Its major determinants are: the volume fraction of red blood cells (haematocrit); plasma viscosity (which is determined mainly by plasma fibrinogen, other biologically reactant globulins, and lipoproteins); red cell deformation (under high flow/shear conditions); and red cell aggregation (under low flow/shear conditions) (Lowe, 1986, 1994). It has been hypothesized that increasing levels of blood viscosity within the general population may promote cardiovascular events through its potential rheological effects on atherogenesis, thrombogenesis, or ischaemia distal to atherothrombotic stenoses or occlusions (Dintenfass, 1971; Lowe, 1986). Recent epidemiological studies have associated blood viscosity with conventional risk factors such as male sex, cigarette smoking, blood pressure, and plasma lipids/lipoproteins (Lowe *et al*, 1988; Lowe, 1994). However, the relationship of blood viscosity to incident cardiovascular events in a large random sample of the general population has not previously been reported.

To test this hypothesis, we measured blood viscosity and its major determinants in the Edinburgh Artery Study (Fowkes *et al*, 1991; Lowe *et al*, 1993), a random sample of men and women aged 55–74 years, and now report their relationships to incident cardiovascular events after 5 years of follow-up. In view of the potential importance of haemorheological variables in cerebrovascular disease in particular (Hartmann & Kuschinsky, 1987), we studied their relationships to stroke, as well as ischaemic heart disease events.

Correspondence: Professor G. D. O. Lowe, University Department of Medicine, Royal Infirmary, 10 Alexandra Parade, Glasgow G31 2ER.

SUBJECTS AND METHODS

Baseline recruitment and examinations. These have previously been reported (Fowkes *et al*, 1991; Lowe *et al*, 1993). Briefly, the Edinburgh Artery Study began in 1988 as a cross-sectional survey of 809 men and 783 women aged 55–74

years, randomly selected in 5-year age bands from 10 general practices serving a range of socioeconomic and geographic areas throughout the city of Edinburgh, Scotland. The questionnaire included validated questions on cardiovascular risk factors including smoking habit, and on cardiovascular history including myocardial infarction, and the World Health Organization questionnaires on angina and claudication. Supine brachial blood pressure was measured after a 10 min rest. A fasting 20 ml arm vein blood sample was taken. Whole-blood and plasma viscosities were measured in EDTA-anticoagulated blood at high shear rates (over 300/s) in a Coulter-Harkness viscometer at 37°C. Haematocrit was measured using a Hawksley microcentrifuge and reader. Blood viscosity was corrected to a standard haematocrit of 45% (Lowe *et al*, 1993). Relative viscosity (haematocrit corrected blood viscosity/plasma viscosity) was calculated as a measure of red cell deformability. Fibrinogen was measured in citrated plasma by a thrombin-clotting turbidometric method (Lowe *et al*, 1993). Serum total and high density lipoprotein (HDL) cholesterol and triglycerides were performed on a Roche Cobas Bioanalyser. Low-density lipoprotein (LDL) cholesterol was calculated using the formula: LDL cholesterol = total cholesterol − HDL cholesterol − triglycerides/5 (Friedewald *et al*, 1972). A 12-lead electrocardiogram (ECG) was taken and coded independently by two observers using the Minnesota code (Prineas *et al*, 1982).

Five-year follow-up. All 1592 study participants were followed for 5 years for cardiovascular events and death. Records were flagged at the U.K. NHS Central Registry to identify deaths. Information on non-fatal events was sought from general practitioners, hospitals, the Information Services Division of the Scottish Office Home and Health Department, and by annual questionnaires to the participants. All cardiovascular events and deaths were further investigated using hospital or general practitioner records. Surviving participants ($n = 1389$) were invited to a 5-year follow-up examination, at which the questionnaire and 12-lead ECG were repeated as at baseline.

Cardiovascular events. Criteria for ischaemic heart disease (IHD) events were adapted from those agreed by the American Heart Association (Gillum *et al*, 1984). Myocardial infarction (MI) was coded if two of the following were present: (i) cardiac pain lasting at least 20 min, (ii) diagnostic or equivocal ECG codes, (iii) elevated or equivocal cardiac enzyme levels. Diagnostic ECG codes in the absence of elevated enzyme levels or cardiac pain were also included (silent MI). Fatal myocardial infarction was recorded if there was post-mortem evidence of acute MI, definite criteria for MI were present within 4 weeks prior to death, or ICD-9 codes for cause of death were 410–414. A diagnosis of new angina pectoris during the follow-up period required that there was no W.H.O. evidence of angina at baseline examination, plus either: (i) positive W.H.O. angina questionnaire and recall of a doctor's diagnosis of angina, or (ii) positive W.H.O. angina questionnaire plus ECG ischaemia, or (iii) clinical diagnosis of angina made following investigation by the general practitioner or in hospital. Coronary artery bypass grafting or angioplasty (coronary revascularization) were coded when these events were noted in participants' records.

Stroke was coded if one of the following criteria were present: (i) onset of symptoms <48 h plus focal or global disturbance of cerebral function lasting >24 h, (ii) computerized tomographic evidence of cerebral infarction or haemorrhage, or (iii) discharge diagnosis included ICD-9 codes 431, 432, 436 or 437. Fatal stroke was coded if therewas post-mortem evidence of cerebral infarction or haemorrhage, criteria for stroke were met within the 6 weeks prior to death, or ICD-9 codes for cause of death were ICD 431–437. Multiple cardiovascular events of the same type occurring in the same subject were reported only once.

Statistical analyses. Data were analysed on the Edinburgh University mainframe computer using SPSS-X and SAS software packages. The cumulative incidence of cardiovascular events was calculated by taking the number of subjects having one or more cardiovascular events as the numerator, and the total initial population as the denominator. Cigarette smoking exposure was calculated in pack-years (years of smoking multiplied by the average number of packs smoked per day) with the value zero entered for lifelong non-smokers. The distribution was highly skewed because there were a few very heavy smokers, and the square root of pack-years was used to reduce the influence of these few individuals. Relative risks using PROC GENMOD from SAS were calculated to determine the strength of the relationship between cardiovascular events and age- and sex-adjusted baseline levels of (a) rheological variables, and (b) conventional risk factors (cigarette smoking exposure, diastolic blood pressure, and LDL cholesterol). In addition, further adjustment was made for conventional risk factors in the case of rheological risk factors; and vice versa.

RESULTS

At the 5-year follow-up examination, comprehensive risk factor information was available on 1287 subjects and there had been 203 deaths. However, all 1592 subjects at baseline had been flagged for death and non-fatal cardiovascular events. 272 subjects with a new cardiovascular event were identified (cumulative 5-year incidence 17·1%). 235 participants had IHD events and 45 had strokes (with eight subjects having both). Among the 272 subjects who had an event, 64·3% were male compared to 48·0% males in the non-event group ($P < 0{\cdot}001$). The mean age of the cardiovascular event group was 66·1 years (SE 0·3) compared to 64·6 years (SE 0·2) in the non-event group ($P < 0{\cdot}001$). All subsequent analyses were therefore adjusted for age and sex. The associations of rheological variables were similar for MI, new angina pectoris, and coronary revascularization events; hence results for all these IHD events were pooled. As in all large epidemiological studies of stroke (Warlow, 1996), it was not possible to confidently distinguish a cerebral haemorrhage group from a cerebral infarction group, due to lack of routine diagnosis by CT scanning or autopsy. In this age-group it is likely that about 85% of strokes are due to cerebral infarction (Warlow, 1996).

Table I. Age and sex adjusted mean (SE) of rheological variables in subjects who experienced cardiovascular events and subjects who did not.

	All events			Ischaemic heart disease			Stroke		
	Yes	No		Yes	No		Yes	No	
Blood viscosity (mPa.s)	3·70 (0·04)	3·55 (0·02)	$P = 0·0003$	3·67 (0·04)	3·56 (0·02)	$P = 0·010$	3·81 (0·09)	3·57 (0·01)	$P = 0·008$
Haematocrit (%)	46·2 (0·21)	45·7 (0·10)	$P = 0·015$	46·1 (0·23)	45·7 (0·09)	$P = 0·15$	46·9 (0·52)	45·7 (0·09)	$P = 0·03$
Corrected viscosity (mPa.s)	3·57 (0·03)	3·48 (0·01)	$P = 0·0025$	3·56 (0·03)	3·48 (0·01)	$P = 0·02$	3·64 (0·07)	3·49 (0·01)	$P = 0·03$
Plasma viscosity (mPa.s)	1·35 (0·006)	1·33 (0·003)	$P = 0·0023$	1·35 (0·006)	1·33 (0·003)	$P = 0·015$	1·37 (0·02)	1·33 (0·02)	$P = 0·03$
Fibrinogen (g/l)	2·88 (0·04)	2·67 (0·02)	$P = 0·0001$	2·86 (0·05)	2·69 (0·02)	$P = 0·0007$	2·96 (0·10)	2·71 (0·02)	$P = 0·016$
Relative viscosity	2·64 (0·02)	2·62 (0·01)	$P = 0·17$	2·64 (0·02)	2·62 (0·01)	$P = 0·26$	2·64 (0·04)	2·62 (0·01)	$P = 0·62$

Table I shows that age- and sex-adjusted mean levels of whole blood viscosity were higher in the subjects who had a new cardiovascular event than in those who did not (3·70 *v* 3·55 mPa.s; $P = 0·0003$). In part, this difference in blood viscosity was associated with a higher haematocrit (46·2% *v* 45·7%; $P = 0·015$); however, haematocrit-corrected blood viscosity remained higher in the event group (3·57 *v* 3·48 mPa.s; $P = 0·0025$). This difference in corrected viscosity was associated with higher plasma viscosity (1·35 *v* 1·33 mPa.s; $P = 0·0023$); which in turn was associated with higher plasma fibrinogen (2·88 *v* 2·67 g/l; $P = 0·0001$). Relative viscosity (a measure of bulk cell deformability) was not significantly higher in the event group (2·64 *v* 2·62; $P = 0·17$).

Separate comparison of subjects who experienced IHD events and those who experienced stroke showed similar relationships to rheological variables, although trends to higher levels of blood viscosity, haematocrit, plasma viscosity and fibrinogen were observed in persons who experienced a stroke (Table I). The relationship of haematocrit to IHD events was not statistically significant ($P = 0·15$).

Table II shows the relative risk of (a) total cardiovascular events, and (b) stroke, associated with a one standard deviation increase in rheological variables. The age- and sex-adjusted relative risk for a one standard deviation increase in blood viscosity (0·58 mPa.s) was 1·20 (95% CI 1·07, 1·36; $P = 0·003$) for cardiovascular events; and 1·41 (95% CI 1·08, 1·85; $P = 0·012$) for stroke. Generally similar relative risks were observed for haematocrit, corrected viscosity, plasma viscosity, and fibrinogen (Table II).

Tables II and III show that the age- and sex-adjusted relative risk of cardiovascular events for rheological variables was stronger than that of cigarette smoking, and similar to the relative risks for diastolic blood pressure and serum LDL cholesterol. When corrected for conventional risk factors as well as age and sex, the predictive value of blood viscosity for cardiovascular events (relative risk 1·13; 95% CI 0·98, 1·29) was no longer statistically significant, suggesting that the association of blood viscosity with events was partly attributable to these risk factors. On the other hand, the association of blood viscosity with stroke was little affected by correction for conventional risk factors (relative risk 1·38; 95% CI 1·03, 1·84); and blood viscosity showed a stronger association with stroke than blood pressure, smoking or cholesterol.

The associations of plasma viscosity and fibrinogen with cardiovascular events and with stroke were little altered followed adjustment for conventional risk factors. These associations were of similar strength to those of diastolic blood pressure or LDL cholesterol for cardiovascular events; and stronger for stroke. The associations of blood pressure and LDL cholesterol (but not cigarette smoking) with cardiovascular events remained significant following adjustment for rheological variables (Table III).

DISCUSSION

We report for the first time that whole blood viscosity is associated with incident cardiovascular events in the general

Table II. Relative risk (95% confidence intervals) of cardiovascular events for a one standard deviation increase in rheological variables. *$P < 0{\cdot}05$, **$P < 0{\cdot}01$, ***$P < 0{\cdot}001$.

	Adjusted for age and sex	Further adjusted for cigarette smoking, diastolic blood pressure and LDL cholesterol
Blood viscosity (SD = 0·58 mPa.s)		
Total events	1·20 (1·07, 1·36)**	1·13 (0·98, 1·29)
Stroke	1·41 (1·08, 1·85)*	1·38 (1·03, 1·84)*
Haematocrit (SD = 3·8%)		
Total events	1·14 (1·00, 1·30)*	1·09 (0·95, 1·26)
Stroke	1·39 (1·03, 1·87)*	1·38 (0·97, 1·86)
Corrected viscosity (SD = 0·41 mPa.s)		
Total events	1·18 (1·04, 1·33)**	1·12 (0·97, 1·28)
Stroke	1·35 (1·02, 1·80)*	1·39 (1·02, 1·89)*
Plasma viscosity (SD = 0·10 mPa.s)		
Total events	1·15 (1·04, 1·27)**	1·17 (1·02, 1·34)*
Stroke	1·26 (1·04, 1·53)*	1·46 (1·06, 2·02)*
Fibrinogen (SD = 0·60 g/l)		
Total events	1·23 (1·11, 1·38)***	1·20 (1·06, 1·35)**
Stroke	1·33 (1·04, 1·71)*	1·33 (1·03, 1·72)*
Relative blood viscosity (SD = 0·26)		
Total events	1·08 (0·95, 1·23)	1·02 (0·89, 1·18)
Stroke	1·09 (0·78, 1·50)	1·09 (0·78, 1·53)

population. Our results suggest that blood viscosity is as strong a predictor of cardiovascular events in the older population as LDL cholesterol or diastolic blood pressure, and is stronger than smoking; that it may be a stronger predictor of stroke than these conventional risk factors; and that plasma viscosity (partly determined by plasma fibrinogen level) may be at least as important as the haematocrit in determining the association between blood viscosity and cardiovascular risk within the population.

The association of blood viscosity and its determinants with incident cardiovascular events in the Edinburgh Artery Study is not explained by baseline ischaemic heart disease, which was unrelated to blood viscosity or its determinants (Lowe *et al*, 1993). The association of a blood test with *incident* cardiovascular events is much stronger evidence for a possible causal role than any association with *prevalent* cardiovascular disease (Meade, 1994). We have previously related blood viscosity and its determinants to age, male sex, smoking, blood pressure, and hyperlipoproteinaemia (Lowe *et al*, 1982, 1988, 1993; Smith *et al*, 1992; Fowkes *et al*, 1993; Lowe, 1994); and its association with cardiovascular events was reduced following adjustment for these. It is therefore likely that part of the association between blood viscosity and incident cardiovascular events reflects

Table III. Relative risk (95% confidence intervals) of cardiovascular events for a one standard deviation increase in conventional risk factors (or 1 unit increase in $\sqrt{}$ pack-years for smoking). *$P < 0{\cdot}05$, **$P < 0{\cdot}01$, ***$P < 0{\cdot}001$.

	Adjusted for age and sex	Further adjusted for blood and plasma viscosity, haematocrit and fibrinogen
Cigarette smoking ($\sqrt{}$ pack-years)		
Total events	1·05 (1·00, 1·09)*	1·03 (0·98, 1·08)
Stroke	1·06 (0·96, 1·18)	1·00 (0·89, 1·13)
Diastolic blood pressure (SD = 12·4 mmHg)		
Total events	1·22 (1·09, 1·37)***	1·19 (1·05, 1·36)**
Stroke	1·28 (0·99, 1·67)	1·21 (0·88, 1·67)
LDL cholesterol (SD = 1·22 mmol/l)		
Total events	1·20 (1·07, 1·35)**	1·17 (1·02, 1·33)*
Stroke	1·05 (0·77, 1·43)	0·98 (0·70, 1·38)

influences of conventional risk factors. On the other hand, the association of blood viscosity with stroke was little affected by adjustment for conventional risk factors. This is of interest because of the direct effects of blood viscosity, haematocrit and fibrinogen on cerebral blood flow (Hartmann & Kuschinsky, 1987).

What is the relative importance of the determinants of blood viscosity for its association with cardiovascular risk? In the current study, 47·6% of inter-individual variance in blood viscosity was attributable to haematocrit, and 20·3% to plasma viscosity: the residual 32·1% is presumably due to red cell deformability and to other influences (Lowe *et al*, 1993).

Haematocrit appeared a weaker associate of total cardiovascular events than blood viscosity, although its association with stroke appeared similar. Recent reports from the British Regional Heart Study (Wannamethee *et al*, 1994a, b) and the Framingham Study (Gagnon *et al*, 1994) support the general epidemiological evidence that haematocrit shows an independent association with IHD and stroke (reviewed in Lowe, 1986, 1994).

On the other hand, correction of blood viscosity to a standard haematocrit of 45% had little effect on its predictive value for cardiovascular events or stroke, and plasma viscosity and fibrinogen showed as strong associations with cardiovascular events and stroke as blood viscosity or haematocrit-corrected blood viscosity. Furthermore, these associations were independent of conventional risk factors. These results are consistent with those of the Caerphilly and Speedwell Collaborative Heart Disease Studies, which also found that plasma viscosity and fibrinogen predicted IHD events in men, independently of conventional risk factors including smoking habit, diastolic blood pressure and cholesterol (Yarnell *et al*, 1991). The correlations of plasma viscosity and fibrinogen were 0·46 in the present study (Lowe *et al*, 1993) and 0·57 in the Caerphilly and Speedwell Studies (Yarnell *et al*, 1991), suggesting that 22–33% of inter-individual variance in plasma viscosity in population samples is attributable to variance in fibrinogen. Lipoproteins also affect plasma and blood viscosity (Lowe *et al*, 1982; Lowe, 1994); however, in the present study LDL cholesterol did not appear a strong determinant of the predictive value of viscosity for cardiovascular events (or vice versa). Seven other studies have shown that plasma fibrinogen is a predictor of cardiovascular events (Wilhelmsen *et al*, 1984; Stone & Thorp, 1985; Meade *et al*, 1986; Kannel *et al*, 1987; Yarnell *et al*, 1991; Ernst & Resch, 1993; Cremer *et al*, 1994; Heinrich *et al*, 1994); the present study suggests that increased blood viscosity may be one mechanism by which hyperfibrinogenaemia (as well as raised haematocrit) may promote cardiovascular events. Finally, increased viscosity may be one explanation for international differences in cardiovascular risk (Koenig *et al*, 1994).

Relative blood viscosity (blood viscosity corrected for both haematocrit and plasma viscosity) was not associated with cardiovascular events, suggesting that decreased red cell deformability was not a major determinant of the predictive value of blood viscosity for cardiovascular events.

We measured blood viscosity at normal body temperature (37°C) and at high shear rates. Under these physical conditions, blood viscosity has a minimum value. Higher blood viscosity values may be expected at low body temperatures (e.g. during the winter season when cardiovascular mortality peaks; Stout & Crawford, 1991; Woodhouse *et al*, 1994); and also under low-shear conditions, as are encountered in areas of the vascular tree where atherogenesis, thrombosis and ischaemia occur (Lowe, 1994). It is therefore conceivable that the associations of blood viscosity with cardiovascular events which we have shown are underestimates of their relationship.

It is possible that the association of fibrinogen (and hence plasma and blood viscosity) with cardiovascular events may arise as a result of hyperfibrinogenaemia due to underlying arterial disease. However, there is increasing evidence that fibrinogen gene polymorphisms are associated with both plasma fibrinogen levels and with arterial disease, suggesting that raised fibrinogen levels may precede arterial disease (Lowe *et al*, 1995). Furthermore, however increased fibrinogen levels arise, there are several plausible biological mechanisms through which high fibrinogen (and hence high viscosity) levels may promote cardiovascular events, including effects on atherogenesis, thrombogenesis, or on ischaemia in the presence of atherothrombotic stenoses or occlusions (Dintenfass, 1971; Lowe, 1986; Lowe *et al*, 1995). Finally, inflammatory states are associated with reduced, rather than increased, haematocrit levels (the 'anaemia of disease'; Lowe, 1987); hence chronic atherosclerotic inflammation cannot explain the contribution of increased haematocrit to increased viscosity in predicting cardiovascular events.

We conclude that increased blood viscosity is associated with cardiovascular events (IHD and stroke) and may be a plausible biological mechanism through which increases in haematocrit, fibrinogen, and other plasma proteins including lipoproteins may promote such events (Dintenfass, 1971; Lowe, 1986, 1994). Reductions in viscosity of potential pathological significance (e.g. corresponding to the mean difference between persons who experience cardiovascular events and those who do not; Table I) can be achieved by either venesection (Turner *et al*, 1988) or by fibrinogen reduction with fibrates (Caimi *et al*, 1988; Bo *et al*, 1991). We suggest that randomized controlled trials of viscosity reduction in the prevention of cardiovascular events – for example, by lowering high levels of haematocrit (Wetherley-Mein *et al*, 1987) or fibrinogen (Lowe *et al*, 1995) – merit consideration. We are currently analysing the relationships of rheological variables to other aspects of cardiovascular disease in this cohort, including sex differences and peripheral arterial disease (Fowkes *et al*, 1994).

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