

Blood and plasma viscosity measurements in patients with glaucoma

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SUMMARY Blood viscosity at 10 shear rates, plasma viscosity, packed cell volume, plasma fibrinogen, serum α_2 -macroglobulin, and serum proteins were measured in 83 patients with low-tension glaucoma (LTG) and 23 patients with 'high-tension glaucoma' (HTG: at least one IOP reading above 40 mmHg) and compared with those in 50 controls. Blood and plasma viscosity values and packed cell volume were significantly higher in the LTG group than those in controls. The HTG and the LTG groups differed only in plasma viscosity, but smoking and drinking habits in the HTG patients were greatly different from those in LTG patients and controls, thus preventing interpretation of data in the HTG group. Within the LTG group viscosity values were highest in a subgroup designated earlier by us as focal ischaemic LTG, whereas another subgroup, senile sclerotic LTG, did not show significant differences compared with controls. These findings may indicate a factor in the pathogenesis of visual field defects and disc cupping in some patients with LTG.

Low-tension glaucoma (LTG), the combination of typical glaucomatous optic disc and visual field changes, an open anterior chamber angle, and comparatively low intraocular pressure is a well recognised entity. Most theories about the pathogenesis of the visual field defects emphasise the importance of high intraocular pressure (IOP) in primary open-angle glaucoma (POAG) and of vascular disease and related risk factors in LTG.¹

Risk factors that have been investigated in LTG include large vessel disease,² hypertension,^{3,4} hypotension and shock,^{5,6} diabetes mellitus,⁷⁻⁹ increased blood lipids,^{10,11} abnormal blood coagulation,¹⁰ and blood pressure in the ophthalmic artery.¹ For none of these factors separately could a strong correlation with LTG be established.

The role of increased blood viscosity is suggested in several disease states with impaired perfusion of tissues, such as myocardial infarction,^{12,13} angina pectoris,¹⁴ intermittent claudication,^{15,16} cerebral infarction,^{17,18} the dementia syndrome,¹⁹ and also in

the microcirculatory disturbances of diabetes mellitus with proliferative retinopathy²⁰⁻²² and retinal vein thrombosis with capillary nonperfusion.^{23,24} In a similar way increased blood viscosity might have a role in the pathogenesis of visual field defects and optic disc cupping in LTG patients, whereas in POAG patients with high IOP the blood viscosity would be expected not to differ much from normal values, because in these patients the high IOP is a far more important factor.

To test this hypothesis we performed blood viscosity measurements on patients at the two extremes of the IOP spectrum and compared these with measurements from controls. We also measured several determinants of blood viscosity.

Patients and methods

Eighty-three unselected patients with LTG and 23 POAG-patients with HTG attending the Eye Departments of the Academic Medical Centre and the St Lucas Hospital were investigated after they had given informed consent. In both groups diagnostic criteria for inclusion were an open anterior

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chamber angle, glaucomatous visual field changes (except in one group suspected of having glaucoma; see below), and glaucomatous disc cupping. Patients with LTG had mean diurnal IOP values of 17 mmHg (maximum 26 mmHg), while those with HTG had at least one IOP reading above 40 mmHg in a diurnal curve. The LTG group was further subdivided into three groups according to previously defined criteria²⁵: a focal ischaemic subgroup (FILTG), a senile sclerotic subgroup (SSLTG), and a miscellaneous subgroup (LTG_{misc}) comprising patients not fitting into either the FILTG or the SSLTG subgroups. In short, criteria for FILTG included an optic disc with local excavation of the neural tissue rim and unipolar vertical elongation, usually with corresponding local peripapillary atrophy; those for SSLTG included a sloping excavation in a pale disc with a moth-eaten aspect combined with extensive choroidal sclerosis and peripapillary atrophy. Patients suspected of having senile sclerotic low-tension glaucoma (SSLTS) had characteristics similar to SSLTG except that they lacked visual field defects.

These groups were compared with 50 controls consisting of ophthalmic patients with normal IOP, normal disc, and normal visual field, who had neither inflammatory nor vascular conditions of the eye. Most controls were admitted for cataract surgery or other elective operations or visited the Outpatient Department for a driving licence examination. None of the patients or controls had any acute illness.

The medical record of all patients was studied and a full medical history was taken, with special emphasis on diseases known to be correlated with high blood viscosity. All patients were questioned about smoking and drinking habits, drug use, and all women about their menstrual cycle.

Blood samples were drawn without venous occlusion by means of a Vacutainer system with a 0.8 mm (21 gauge) needle. Viscosity measurements were done on blood anticoagulated with dry EDTA (1 mg/ml) within five hours of sampling. The measurements were carried out with the Contraves Low Shear 30 viscometer by means of a standardised computer directed protocol described elsewhere.²⁶ Temperature was kept constant at 37°C. Whole blood viscosity was measured at 10 shear rates covering the entire physiological range. Plasma viscosity was measured at five shear rates, and if the values obtained showed newtonian behaviour the plasma viscosity was calculated as the mean of the five measurements. Haemoglobin, packed cell volume (PCV), and thrombocyte count were measured on a Haemalog 94 apparatus using blood anticoagulated in EDTA (1 mg/ml); in this apparatus a microcentrifuge technique is used for measurements of the PCV. Blood was anticoagulated with

trisodium citrate (0.1 ml/ml) for measurement of plasma fibrinogen by a quantitative biuret method.²⁷ A standard photometric method was used for determination of total serum protein. Serum protein electrophoresis was carried out according to standard methods. Serum α_2 -macroglobulin was estimated immunochemically.

As a normal distribution of the results could not be assumed, statistical analysis of differences between groups was performed by the Wilcoxon sum of ranks test.

Results

COMPARABILITY OF PATIENT GROUPS

The LTG group and the control group proved to be comparable with regard to several important clinical characteristics (Table 1). Differences were seen in the prevalence of diabetes mellitus and paraproteinaemia. Diabetes mellitus occurred more frequently in the controls with higher than mean blood and plasma viscosity. Exclusion of these persons from the control group would lower the mean plasma and blood viscosity values and hence would make differences between glaucoma patients and controls larger. Furthermore, no significant difference in the other parameters measured was found between controls with and without diabetes mellitus. For these reasons we did not exclude persons with diabetes mellitus from the control group.

In none of the groups did the occurrence of paraproteinaemia raise significantly the mean values of the blood or plasma viscosity.

The HTG group on the other hand did show some important differences compared with the other groups. The mean age was about 14 years lower; none of the patients gave a history of vascular disease; the consumption of alcohol and tobacco was much higher than in either the LTG or the control group (Table 2).

The mean age (\pm SD) of the patients in the SSLTG and SSLTS subgroups proved to be 82.1 (\pm 5.2) years

Table 1 Clinical features in patient groups

	Controls	LTG	HTG
Number	50	83	23
Age \pm SD (yr)	74.7 (8.9)	73.9 (10.3)	60.6 (7.7)
Males	19	35	14
Hypertension (%)	27	30	20
Diabetes mellitus (%)	23	9	8
Ischaemic vascular disease (%)	25	20	0
Chronic pulmonary disease (%)	8	8	4
Venous thrombosis (%)	10	10	8
Paraproteinaemia (%)	2	7	8

Table 2 Drug use, smoking, and drinking habits in patient groups

	Controls	LTG	HTG
β-blockers (%)	12	10	8
Diuretics (%)	27	23	16
Other antihypertensives	8	12	10
NSAID (%)	12	13	4
Coumarins (%)	10	15	0
Oral contraceptives (%)	0	0	4
Smokers (%)	14	18	74
Cigarettes/week pp	30	55	70
Drinkers (%)	33	48	72
Glasses per week per patient	8	8	10

NSAID=non-steroidal anti-inflammatory drugs.

and 79.0 (±11.8) years respectively, significantly higher than controls. We therefore compared these two subgroups with a subgroup of controls of about the same age (mean age 82.8±4.0 years, n=21). The other two LTG subgroups were comparable in age with the control group (73.9±9.0 years and 70.9±10.1 years for FILTG and LTG_{misc} respectively).

MEASUREMENT RESULTS

Blood viscosity at 10 shear rates was significantly higher than controls in both the HTG group and the LTG group as a whole. In the LTG group only the focal ischaemic subgroup showed significant differences over the whole range of shear rates (Table 3). Mean whole blood viscosity in the FILTG subgroup was 22% higher than in controls at the lowest shear rate and 10% at the highest shear rate. The LTG_{misc} subgroup differed significantly from controls at nine shear rates, but the differences were less than in the FILTG subgroup. The SSLTG and SSLTS subgroups did not show any significant difference from a subgroup of controls of about the same age at the 10 shear rates measured, even though values in the

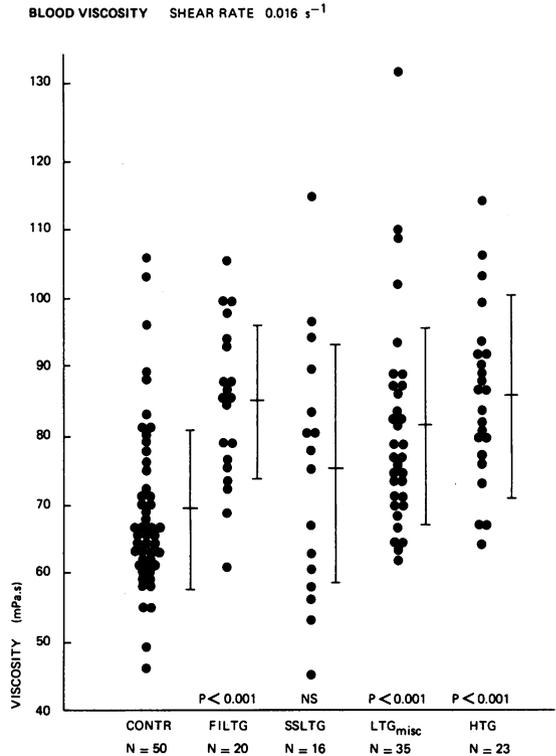


Fig. 1 Whole blood viscosity results in patient groups and controls at the lowest shear rate measured. Mean, standard deviation, and p value for difference from controls are indicated.

latter were somewhat lower than in the control group as a whole.

In all groups the greatest differences were at the low shear rates. Figs. 1 and 2 illustrate the viscosity results at the lowest and the highest shear rates measured respectively.

Table 3 Blood viscosity at 10 shear rates in patient groups and controls. Values are means ± standard deviation, expressed in mPa.s (1 mPa.s=1cP)

Shear rate (s ⁻¹)	Controls (n=50)	Total LTG (n=83)	FILTG (n=20)	SSLTG (n=16)	SSLTS (n=8)	LTG _{misc} (n=35)	HTG (n=23)
0.016	69.6±12.0	80.1±14.5***	84.7±11.5***	75.8±17.2	80.8±16.2*	80.8±14.2***	85.2±14.3***
0.040	56.2±10.0	64.9±11.4***	68.4±8.9***	61.9±13.5	65.2±14.0*	65.2±11.0***	68.2±9.8***
0.101	40.9±7.5	47.4±8.5***	50.2±6.6***	45.1±10.1	47.5±10.2*	47.4±8.4***	50.0±6.9***
0.255	28.4±5.3	32.9±6.0***	34.9±4.6***	31.6±7.2	32.9±7.1*	32.7±6.0***	34.9±4.9***
0.640	19.3±4.1	22.2±4.6***	23.3±3.4***	21.9±5.5	22.3±5.9	22.0±4.7**	23.3±3.4***
1.607	13.3±2.9	15.1±3.0***	15.9±2.2***	14.8±3.5	15.2±3.6	15.1±3.1**	15.9±2.3***
4.037	9.6±1.9	10.9±2.0***	11.3±1.4***	10.7±2.2	11.0±2.4	10.8±2.1**	11.4±1.5***
10.142	7.2±1.3	8.0±1.3***	8.3±0.9***	7.9±1.4	8.1±1.6	8.0±1.3**	8.3±1.0***
34.629	5.4±0.7	5.8±0.7**	5.9±0.5**	5.7±0.8	5.8±0.9	5.7±0.8	6.0±0.5***
118.242	4.2±0.5	4.5±0.5**	4.6±0.4**	4.4±0.6	4.5±0.7	4.5±0.6*	4.6±0.4**

*p<0.05 (vs. controls, Wilcoxon test).

**p<0.01 (vs. controls, Wilcoxon test).

***p<0.001 (vs. controls, Wilcoxon test).

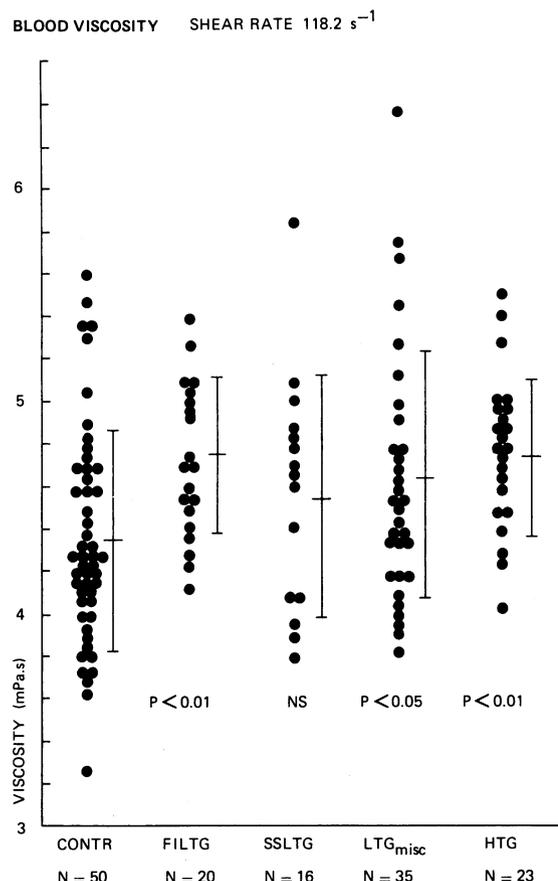


Fig. 2 Whole blood viscosity results in patient groups and controls at the highest shear rate measured. Mean, standard deviation, and p value for difference from controls are indicated.

Mean plasma viscosity was significantly higher than in controls in the LTG group but not in the HTG group. Again within the LTG group a statistically significant difference was evident only in the FILTG and LTG_{misc} subgroups (Fig. 3). The packed cell volume was significantly higher in both the LTG and the HTG group than in the controls; in the LTG group the higher level was confined to the FILTG and LTG_{misc} subgroups (Fig. 4).

As to the other parameters measured, including plasma fibrinogen and α_2 -macroglobulin, no statistically significant differences between the groups were detected (Table 4).

Discussion

This study shows that patients with LTG have a significantly higher whole blood viscosity measured over the whole range of physiological shear rates

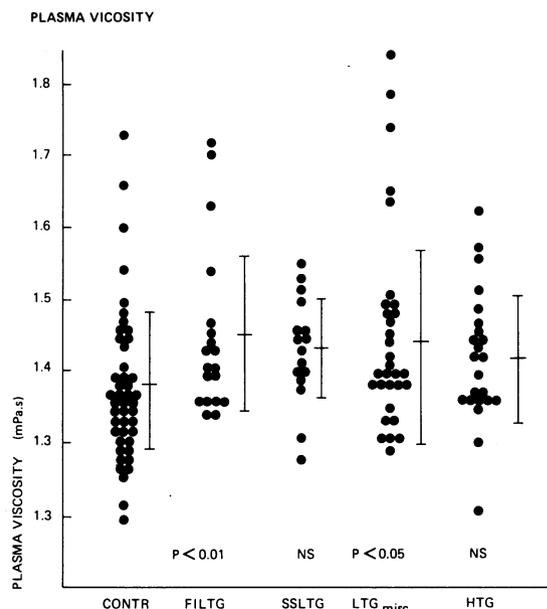


Fig. 3 Plasma viscosity results in patient groups and controls. Mean, standard deviation, and p value for difference from controls are indicated.

when compared with a control group matched for age, sex, and several important clinical features that influence blood viscosity. The increased viscosity was associated partly with increased packed cell volume and partly with increased plasma viscosity. It may be questioned whether a group of cataract patients is a suitable control group. The fact that the frequency of general cardiovascular disease in the LTG group and the cataract group is comparable is in favour of the selection of the cataract group as control. One could

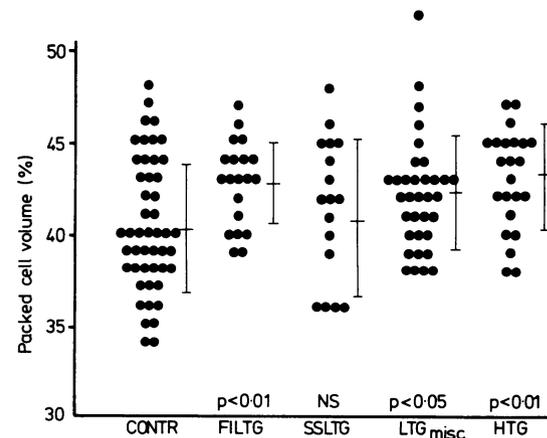


Fig. 4 Packed cell volume results in patient groups and controls. Mean, standard deviation, and p value for difference from controls are indicated.

Table 4 Plasma viscosity and blood, serum, or plasma concentrations of the other variables measured. Values are means ± standard deviation

	Controls (n=50†)	Total LTG (n=83)	FILTG (n=20)	SSLTG (n=16)	SSLTS (n=8)	HTG (n=23)
Plasma viscosity (mPa.s)	1.38±0.10	1.43±0.12*	1.45±0.12*	1.43±0.07	1.42±0.08	1.41±0.09
Haemoglobin (mmol/l)	8.7±0.79	9.0±0.80*	9.2±0.46*	8.9±1.04	8.8±0.81	9.4±0.74*
Haematocrit (%)	40.3±3.59	41.9±3.27*	42.8±2.20**	40.8±4.26	40.6±4.18	43.1±2.95*
Fibrinogen (g/l)	2.74±0.59 (n=17)	2.77±0.84	2.80±0.70	2.98±0.68	2.73±0.60	2.89±0.86
α ₂ -macroglobulin (g/l)	3.11±1.03	3.06±0.70	3.11±0.72	3.06±0.93	3.22±0.87	2.64±0.83
Total serum Protein (g/l)	67.7±5.7	70.2±4.9	70.2±4.1	71.7±3.9	69.3±4.5	70.3±4.9
Albumin (g/l)	39.3±2.7	41.1±5.1	41.8±3.4	41.0±2.3	40.8±2.0	41.4±2.7
α ₁ -globulin (g/l)	2.16±0.44	2.23±0.59	2.20±0.62	2.37±0.52	2.29±0.32	2.28±0.53
α ₂ -globulin (g/l)	6.93±1.39	7.13±1.41	7.31±1.36	7.62±1.09	7.11±1.48	7.34±1.54
β-globulin (g/l)	7.65±1.07	7.92±1.29	7.86±1.08	8.28±1.27	7.66±1.38	8.08±1.58
γ-globulin (g/l)	11.7±4.0	11.3±3.2	11.1±3.12	12.4±2.32	11.3±2.61	11.5±3.4
Thrombocytes (× 10 ⁹ /l)	233±46	250±60	259±65	241±37	237±80	281±82

†Only 17 control values of fibrinogen were available.

*p<0.05 (vs. controls, Wilcoxon test).

**p<0.01 (vs. controls, Wilcoxon test).

argue that cataract is an eye disease that may in itself be related to viscosity. Even if this were so the outcome would be influenced only in a negative way. One would then expect the differences between LTG and a completely normal age matched group to be even greater. We were unable to show a difference in whole blood viscosity between LTG and HTG patients. In fact the HTG patients in our study had whole blood viscosity values similar to those of the LTG subgroup with the highest blood viscosity results. The high blood viscosity in the HTG group was not associated with increased plasma viscosity, and a high packed cell volume appeared to be the dominant factor involved. This may be explained by the large tobacco consumption in the HTG group as compared with the other groups. Owing to this difference in smoking habits in our series a valid conclusion as to the original hypothesis, namely, that blood viscosity in LTG patients will be higher than in HTG patients, cannot be drawn.

These results are suggestive of increased whole blood viscosity being a risk factor for glaucomatous optic nerve damage in at least some patients with LTG, notably those subclassified by us as belonging to the focal ischaemic subgroup. It is interesting that two subgroups of LTG could be identified by ophthalmoscopy that show significant differences in blood viscosity. Without a subclassification of LTG these differences would have been overlooked. This emphasises the necessity of subclassification in research into the pathogenesis of LTG. There is evidence that local disturbance of the microcirculation at the disc is an important damaging factor in FILTG. Fluorescein angiography in these patients frequently shows inferotemporally localised, sharply defined filling defects of the optic disc, while the

remainder of the disc appears well vascularised.²⁸ From a theoretical point of view the role of high blood viscosity, especially at low shear rates, in the pathogenesis of glaucomatous optic nerve damage would be obvious.

In normal circumstances the major factors in the microcirculation are the autoregulation of the vascular diameter and the perfusion pressure, blood viscosity playing a minor role. However, blood is a fluid with non-newtonian behaviour, which implies that blood viscosity varies with the force applied to it. The rheological term 'shear rate' is often used in this context, high shear rate being present when flow is fast and the vessel diameter small, and low shear rate present when flow is slow and the vessel has a large diameter. The non-newtonian behaviour of blood is due to the tendency of red cells to aggregate at low shear rates when low shear forces are applied to them, while these aggregates disperse when the shear forces become higher. Furthermore, when shear rates are high the red cells are deformed to become optimally adapted to the flow conditions. Normally in the capillaries high shear rates occur and blood viscosity will be low, but, as flow is chronically retarded, irrespective of the causative factor shear rates will fall and blood viscosity will rise, resulting in still further decreasing flow. Thus when vasomotor reserve becomes exhausted, even slightly increased viscosity may become a critical and limiting factor governing flow.²⁹

There is evidence that increased blood viscosity plays a role in capillary non-perfusion associated with retinal vein occlusion^{23,24} and diabetic retinopathy.²⁰⁻²² The angiographic findings in FILTG patients suggest localised capillary non-perfusion of the disc. The fact that there is a predilection for the inferotemporal

margin of the disc may be due to some anatomical peculiarity of the vascularisation to that area. According to the above theoretical considerations patients with increased blood viscosity would be at great risk of developing decompensation of the microcirculation, viscosity not being the initiating but an aggravating factor, setting into motion a vicious circle of decreasing flow, which leads to higher viscosity, which then further slows down flow, and so on.

In the senile sclerotic LTG subgroup, in which no increase of blood viscosity could be demonstrated, senile atrophy probably owing to generalised vascular disease was proposed earlier as a pathogenic mechanism.²⁵ The same goes for the SSLTG subgroup.

Finally the LTG_{misc} subgroup, which is a collection of patients that could not be classified into either the FILTG or the SSLTG subgroup, has viscosity values that lie in between those for FILTG and SSLTG, possibly reflecting its heterogeneity.

Prospective studies are needed to establish more clearly the role of high blood viscosity in the development of glaucomatous optic nerve damage. If a causative role of high blood viscosity can be demonstrated, this finding would have therapeutic consequences, since several drugs have been shown to be effective in lowering blood viscosity.

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