

Pulsatile ocular blood flow in patients with low tension glaucoma

C B James, S E Smith

Abstract

Measurements of the intraocular pressure (IOP) pulse and pulsatile ocular blood flow (POBF) have been made in 22 patients with bilateral low tension glaucoma (LTG) and 29 healthy subjects matched as closely as possible for age, refractive error, IOP, systemic pulse pressure, and heart rate. Recordings were made in both the standing and supine positions. The amplitude of the intraocular pressure pulse was significantly lower in patients with LTG (1.2, SEM 0.1 mmHg standing, and 1.3, SEM 0.1 mmHg lying) than in healthy subjects (1.9, SEM 0.1 mmHg standing, and 2.0 SEM 0.1 mmHg lying): $p < 0.001$ standing and $p < 0.002$ lying. Measurement of POBF also showed a significant reduction between the healthy subjects (428 (31) SEM $\mu\text{l}/\text{min}$ standing and 345 (28) SEM $\mu\text{l}/\text{min}$ lying) and subjects with LTG (301 (27) SEM $\mu\text{l}/\text{min}$ standing and 249 (24) SEM $\mu\text{l}/\text{min}$ lying), $p < 0.005$ standing and $p < 0.02$ lying. This represents a difference of approximately 30% between the two groups in either posture. A close non-parametric correlation existed between the level of IOP and the POBF ($r = 0.75$, $p < 0.001$ standing, and $r = -0.55$, $p < 0.02$ lying). Such a correlation was not present in the healthy subjects. A reduction in POBF occurred in both groups on assuming the supine posture (healthy subjects 83 (16) SEM $\mu\text{l}/\text{min}$, LTG subjects 52 (17) SEM $\mu\text{l}/\text{min}$). These figures represent reductions of 19% and 17% respectively in comparison with the standing value. The results lend further confirmation to the hypothesis that vascular factors are associated with low tension glaucoma.

Low tension glaucoma (LTG) can be defined as the development of typical glaucomatous optic disc cupping and field damage in patients with normal iridocorneal angles and intraocular pressure (IOP) within the statistically normal range. Some regard the condition as separate from chronic open angle glaucoma (COAG), whereas others regard it as representing one end of the glaucoma spectrum.¹ Much interest has centred on the vascular origins of LTG. In an extensive review Levene examined the role of systemic hypertension, generalised vascular disease, reduced ophthalmic artery pressure, and retinal vascular occlusion.² He concluded that the evidence of an association with any of these factors is at best uncertain. Subsequent work has confirmed this view.³

Better evidence exists for small vessel occlusion producing a sector infarct of the optic nerve linked to the presence of a splinter haemorrhage.^{2,4} An increased incidence of migraine,^{5,6} a

reduced response of peripheral blood flow to cold,⁷ and a reduced compliance of the optic nerve head to a raised IOP measured by the visual evoked response⁸ have also been reported. Schulzer *et al* have recently suggested that in both LTG and COAG there may be two groups of patients – one with predominantly IOP related disease and one with vascular disease.⁹ These observations lend further corroboration to the theory that reduced perfusion, however caused, is at least a factor in the pathogenesis of LTG.

Clinical assessment of blood flow in the eye and optic disc has depended on the analysis of fluorescein angiograms. In both COAG and LTG hypofluorescence of the disc and prolonged fluorescein transit times have been reported.¹⁰⁻¹² Hypofluorescence is more likely to be focal in LTG.¹⁰ A prolongation in transit time and choroidal filling have also been reported in patients with progressive LTG in comparison with those in whom the visual field defect did not appear to progress.¹³

An additional method for the examination of ocular pulsatile bloodflow is available. The ocular pressure pulse originates from blood filling the choroidal vasculature during cardiac systole.¹⁴ The intraocular pressure pulse has been observed to be reduced in patients with LTG.¹⁵ A method of analysis of the ocular pulse has been devised which converts the pressure pulse into a volume pulse, and with knowledge of the heart rate a measure of the pulsatile ocular bloodflow (POBF) can be calculated.^{16,17} As the choroidal and anterior optic disc circulations share a common source from the posterior ciliary arteries a reduction in choroidal circulation may well reflect a reduction in optic nerve head perfusion. Altered choroidal circulation is not, however, the only factor that will affect the intraocular pressure pulse. Additional factors include the initial level of IOP,¹⁸ the systemic pulse pressure,¹⁹ and, as shown by recent work in this department, the ocular volume and the heart rate. The aim of this study was to measure the ocular pulse and the derived POBF in patients with LTG and compare the results with those obtained in a group of healthy volunteers matched as closely as possible for the factors outlined above.

Material and methods

PATIENTS AND VOLUNTEERS

Twenty-two patients, 12 male and 10 female, with bilateral LTG were examined in this study. Low tension glaucoma was diagnosed if the patient had typical glaucomatous cupping, glaucomatous field defects, normal iridocorneal angles on gonioscopy, and no IOP off treatment

Division of
Pharmacological
Sciences and Toxicology,
United Medical and
Dental Schools of Guy's
and St Thomas's
Hospitals, St Thomas's
Hospital, London
SE1 7EH
C B James
S E Smith

Correspondence to:
Mr C B James, Department of
Clinical Pharmacology, St
Thomas's Hospital, London
SE1 7EH

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greater than 22 mmHg during either day or 24-hour phasing. No patient had any neurological deficit. One patient with a cataract extraction but no patients with trabeculectomy were included in this study. One patient was observed to have slight senile macular changes on fundal examination. Ten patients taking topical ocular hypotensive medication stopped this for two weeks prior to measurement. Two patients were taking systemic B adrenoceptor blocking drugs, one was taking systemic B adrenoceptor blocking drugs and isosorbide dinitrate, three were taking nifedipine, two were on thiazide diuretics, and two were on digoxin.

Twenty-nine healthy volunteers, six male and 23 female, on no medication and with no significant past ocular history, matched as closely as possible for age, refractive error, IOP, systemic pulse pressure, and heart rate, were measured as a control group. Table 1 outlines these variables for the two groups. Written consent was obtained from each subject after full explanation of the procedure had been given. Measurements were performed randomly in both groups between the hours of 0900 and 1800.

MEASUREMENTS

Intraocular pressure and the ocular pulse were measured in both eyes with a pneumotonometer linked to a Langham Ocular Blood Flow System after instillation of local anaesthetic (benoxinate). Heart rate was determined simultaneously with an electrocardiograph (ECG). The POBF was calculated as previously described.^{20 21}

The blood pressure was recorded with an autosphygmomanometer (Takeda Medical) and an arm cuff level with the heart in both upright and supine postures. The mean blood pressure was calculated as diastolic pressure + 1/3 of the pulse pressure.

The following protocol was observed for both groups of subjects. Refractive and slit-lamp examination and funduscopy were first performed on all subjects. Prior to measurement the subject rested seated for 10 minutes. This was followed by a period of 5 minutes standing. Measurement of blood pressure and pneumotonometer recordings were then made. The subject then lay down for 15 minutes using one pillow as a headrest, and the procedure was repeated. The pneumotonometer calibration was checked immediately before each patient was measured and at each change in posture.

Table 1 Characteristics of the two study groups

	Healthy subjects		Low tension glaucoma		p
	Mean (SEM)	Range	Mean (SEM)	Range	
Age (yr)	51 (1.8)	29/73	70.3 (2.3)	48/87	0.0001
Refraction (dioptres)	0 (0.3)	-5.5/2.7	-0.3 (0.6)	-7.75/4	NS
Standing IOP (mmHg)	17.4 (0.3)	11.4/23.2	17.8 (0.5)	12.4/21.1	NS
Lying IOP (mmHg)	19.6 (0.6)	13.9/26.8	20.5 (0.5)	15.6/25.4	NS
Standing MBP (mmHg)	99 (2)	81/126	105 (3)	82/129	NS
Lying MBP (mmHg)	90 (2)	75/125	99 (3)	80/130	0.02
Standing SPP (mmHg)	46 (3)	24/119	54 (4)	23/81	NS
Lying SPP (mmHg)	47 (2)	24/94	52 (3)	31/78	NS
Standing HR (bpm)	70 (1)	58/86	79 (4)	49/114	0.02
Lying HR (bpm)	59 (1)	48/74	66 (3)	48/93	0.03

MBP=mean blood pressure. SPP=systemic pulse pressure. HR=heart rate.

Table 2 Mean (SEM) for the ocular variables measured in upright and supine postures

	Healthy subjects		LTG subjects	
	Standing	Lying	Standing	Lying
Pulse amplitude mmHg	1.9 (0.1)	2.0 (0.1)	1.2 (0.1)	1.3 (0.1)
Pulse volume (µl)	6.0 (0.5)	5.7 (0.4)	3.9 (0.3)	3.8 (0.34)
POBF µl/min	428 (31)	345 (28)	301 (27)	249 (24)

STATISTICAL ANALYSIS

Differences between subjects were assessed with unpaired *t* tests. Within-subject differences were analysed with paired *t* tests. Spearman's non-parametric regression analysis was used to determine the relationship between IOP and POBF in both groups.

Results

DIFFERENCES BETWEEN GROUPS

No significant difference was found between the right and left eyes in either of the two groups; thus only the results for the right eyes will be quoted. The results of the ocular pulse and POBF measurements are shown in Table 2. There was a significant difference in the amplitude of the ocular pulse between the two groups of 0.7 mmHg standing and lying (*p*<0.001 standing, *p*<0.002 lying) (Fig 1). Similarly the ocular pulse volume was significantly less in the LTG group by 2.1 µl standing and 1.9 µl lying (*p*<0.001 standing and *p*<0.01 lying). The POBF was also significantly reduced in the patients with LTG, 127 µl/min standing and 96 µl/min lying (*p*<0.01 and *p*<0.02 respectively) (Fig 2). This represents a lower POBF in patients with LTG than was seen in healthy subjects of approximately 30% in either posture.

A significant non-parametric relationship existed between IOP and POBF in the subjects with LTG (*R*=-0.75, *p*<0.001 standing, *R*=0.55, *p*<0.02 lying) (Fig 3). No such relationship was seen in the healthy subjects (*R*=0.16, NS standing, *R*=0.06, NS lying) (Fig 4).

POSTURAL DIFFERENCES

There was a significant increase in IOP on assumption of the supine position (2.7 (SEM 0.3) mmHg, *p*<0.001 in the LTG subjects, and 2.2 (SEM 0.4) mmHg, *p*<0.001 in the healthy subjects), but the difference between the two

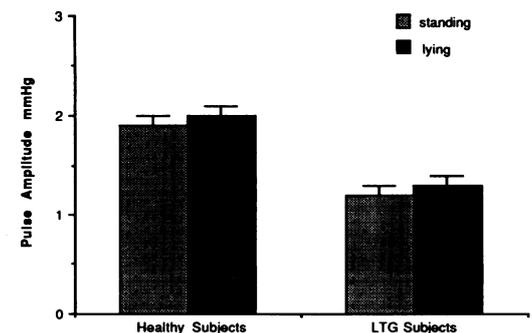
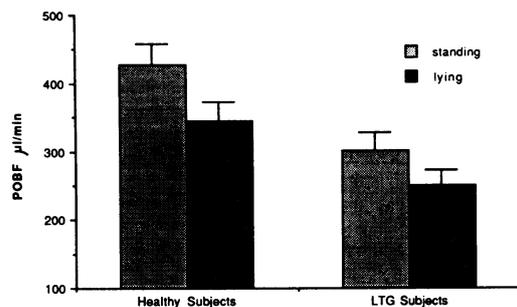


Figure 1 Pulse amplitude in healthy subjects and those with LTG showing the effect of postural change.

Figure 2 POBF in healthy subjects and those with LTG showing the effect of postural change.



groups was not significant. The pulse amplitude in the LTG subjects increased slightly on lying (0.1 (SEM 0.1) mmHg, $p < 0.05$), but no other significant postural changes in the characteristics or derivatives of the ocular pulse was seen in either of the groups (Table 2). A reduction in POBF was seen on lying down in both healthy subjects (83 (SEM 16) $\mu\text{l}/\text{min}$ $p < 0.001$) and in the LTG subjects (52 (SEM 17) $\mu\text{l}/\text{min}$, $p < 0.006$) (Fig 2). This represented a reduction in flow of 19% and 17% ($p < 0.001$ and $p < 0.006$) respectively.

Postural changes occurred in both groups in mean blood pressure (9 (SEM 1) mmHg healthy subjects $p < 0.001$, 6 (SEM 2) mmHg in the LTG group $p < 0.002$) and heart rate (11 (SEM 1) bpm, $p < 0.001$ in healthy subjects, 13 (SEM 2) bpm, $p < 0.001$ in the LTG group). There was no significant postural change in the systemic pulse pressure.

Discussion

Our results show that there is an overall reduction in ocular pulse amplitude, pulse volume, and POBF in subjects with LTG in comparison with a normal volunteer control group. Previous measurements of the ocular pulse amplitude in LTG have been inconclusive. Perkins reported a reduction in the ocular pulse amplitude.¹⁵ Lambrou *et al* found no difference in the pulse amplitude but did find a reduction in pulse volume measurements in subjects with LTG.²² Comparison of ocular pulse measurements between groups is complicated by the numerous factors which may alter ocular pulse amplitude other than the pulsatile flow of blood into the choroidal vasculature. Initial IOP, ocular volume, and heart rate will all affect the size of the ocular pressure pulse. A correlation between

Figure 3 The relation between IOP and POBF in LTG subjects.

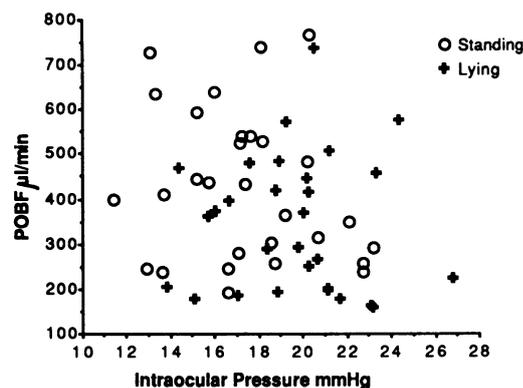
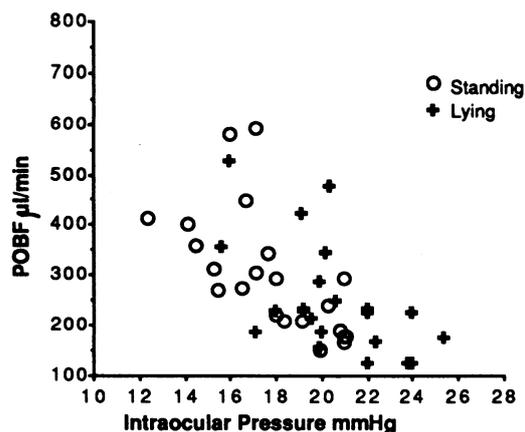


Figure 4 The relation between IOP and POBF in healthy subjects.

systemic pulse pressure and ocular pulse amplitude has also been reported.¹⁹ We have attempted to match these variables in the two study groups. Intraocular pressure in the two groups was similar. Refractive error was also similar. Refractive error if axial will be proportional to the length of the eye and hence if the eye is assumed to be spherical will be proportional to ocular volume. Tomlinson and Leighton²³ found no significant difference in axial length between normal subjects and LTG patients with equivalent refractions. Matching for refractive error should ensure matching for ocular volume.

In our study the LTG subjects differed from their controls in two respects. First, they were older by 19 years. No significant changes in choroidal blood flow with age, by indocyanine green dye methods to measure blood flow, have been demonstrated unless macular degenerative changes are present.²⁴ Only one LTG subject in this study had slight macular changes. An alteration in scleral rigidity will affect the size of the ocular pulse and calculations made from it. Slight changes do occur with age, though there is considerable variation.²⁵ It is not likely that a change in scleral rigidity over the age difference seen here would be significant. Secondly, the LTG subjects had a slightly faster pulse rate (Table 1). This would tend to increase rather than reduce POBF but may reduce the amplitude of the pulse pressure. For the difference in heart rate observed the difference would be only small. It thus appears reasonable to assume that the observed differences between groups are not artifactually caused by differences in systemic or ocular factors not directly related to pulsatile ocular blood flow but reflect a real reduction in both the ocular pulse amplitude and POBF in patients with LTG. These results compare with measurements made in patients with COAG, where a reduction of POBF was found, though to a lesser degree, than were found in the LTG patients in this study.²¹

The importance of vascular factors in the aetiology of both LTG and COAG has been debated for many years.²⁶⁻²⁸ Pathologically there is a decrease in the vascularity of the optic disc in glaucomatous eyes.^{29,30} It is impossible to know whether this is a result or cause of glaucomatous optic nerve damage, however. Much experimental work has centred on the effect of raised IOP as a means of altering the perfusion pressure of the optic nerve.³¹⁻³⁴ This suggests that optic

nerve blood flow is not affected until the IOP is significantly raised – that is, the circulation displays autoregulation. Experiments in primates show that the chronic glaucoma model is associated with the same pattern of nerve fibre loss as is seen in human glaucoma.³⁵ Studies with tritiated iodoantipyrine³² on this model have, however, failed to show a significant reduction in optic nerve blood flow. This work has been performed in previously healthy animal eyes, and care must be taken in interpreting the findings in the human glaucomatous eye, where, for example, autoregulation of optic nerve blood flow may be deficient or a reduction in optic nerve blood flow may be a second and independent factor in the aetiology of glaucomatous damage. Examination of the metabolic function of the optic nerve head³⁶ has shown that relatively small changes in mean arterial pressure or increases in IOP may result in metabolic dysfunction of the optic nerve head which appear to be ischaemic in origin. Chronic reduction of ocular blood flow despite an IOP within the statistically normal range may thus result in metabolic or ischaemic damage to the optic nerve head. The finding in this study of a reduced POBF in LTG is therefore of great interest, as it suggests that eyes with LTG may indeed be susceptible to chronic metabolic dysfunction.

The measurement of POBF is essentially one of choroidal rather than anterior optic nerve blood flow. Although both circulations are derived from the posterior ciliary supply,³⁷ caution must be used in drawing conclusions on anterior optic nerve blood flow from choroidal flow which appears not to demonstrate autoregulation.^{38,39} Measurement of pulsatile blood flow will also not take account of any non-pulsatile flow that may be present. Doppler studies have revealed moving blood in the ophthalmic artery during diastole,⁴⁰ though the extent to which such non-pulsatile flow contributes to total perfusion of the optic nerve head is at present unknown.

The close relationship between IOP and POBF seen in this study is also of particular interest (Fig 3). A relationship between asymmetric glaucomatous damage with asymmetric IOP has been reported, the eye with the higher pressure suffering the most damage.⁴¹⁻⁴² Our findings suggest that as well as a relatively elevated IOP these eyes may also suffer from a reduced pulsatile blood flow.

A postural reduction in POBF was seen in both groups of subjects. The relationship between pulsatile and non-pulsatile flow may also be affected by postural change, however. Perfusion pressure will alter on assumption of the supine posture. A rise in IOP and venous pressure and a fall in mean blood pressure (Table 1) will reduce perfusion pressure, but a larger fall in arterial hydrostatic pressure will increase perfusion pressure. An observed postural increase in ophthalmic perfusion pressure of 10 mmHg⁴³ fits well with these changes. An increase in the ophthalmic artery blood velocity during diastole has also been reported.⁴⁰ One might thus expect to see an increase in non-pulsatile flow in the supine position. The relationship for total blood flow is more complex,

for this is also determined by pulse rate, which decreases in the supine position (Table 1). At decreased pulse rates not only would total blood flow fall but the proportion of pulsatile to non-pulsatile flow would be expected to increase. These complex relationships make it difficult to assess whether the fall in POBF reflects a postural fall in total blood flow or not. During sleep, however, when heart rate and mean arterial pressure fall further, an already reduced ocular circulation may be compromised.

Conclusion

Using a pneumotonometer linked to a Langham Ocular Bloodflow system we have recorded the ocular pulse in a group of subjects suffering from LTG and a carefully matched control group. Using previously established techniques we have derived a measure of the POBF in both groups. A significant reduction in both the ocular pulse amplitude and the POBF has been found in patients suffering from LTG. In both groups there was a significant reduction in POBF on lying. In LTG subjects a close correlation between IOP and POBF was found. These results lend further weight to the theory that vascular factors are associated with the development of LTG and critical underperfusion is causative of damage to the optic nerve head, particularly when the subject is supine. Further research to elucidate the effect of reducing IOP on blood flow in these patients and to determine methods of improving ocular blood flow may be helpful in treating this condition.

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