REDUCED OCULAR PULSE AMPLITUDE IN LOW TENSION GLAUCOMA IS INDEPENDENT OF VASOSPASM

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SUMMARY

Purpose: A vascular basis for the pathogenesis of primary open angle glaucoma has been postulated for many years. Defects in the regulation of ocular blood flow may be the initiating factor in this group of multifactorial diseases. This study was designed to evaluate the effect of vasospasm on ocular pulse amplitude (OPA) in low tension glaucoma (LTG) patients.

Methods: OPA, using the Langham Ocular Blood Flow (OBF) System, applanation intraocular pressure (IOP), systemic blood pressure and heart rate were measured and vasospasm was determined by a fingernail capillary blood flow test.

Results: OPA (mmHg) in the LTG patients with a vasospastic reaction (LTG-V, 1.4 ± 0.1 , $n = 17$) was not significantly ($p > 0.09$) different when compared with non-vasospastic LTG patients (LTG-NV, 1.5 ± 0.2 , $n = 15$) but was significantly ($p < 0.001$) reduced in LTG-V and LTG-NV patients when compared with matched healthy control subgroups (2.3 ± 0.2 and 2.4 ± 0.3 , respectively). IOP (mmHg) in LTG-V (13.3 ± 0.4) and LTG-NV (13.2 ± 0.5) patient groups was not significantly ($p > 0.05$) different when compared with each other, but was significantly ($p < 0.05$) lower when compared with matched control subgroups (15.0 ± 0.3 and 15.2 ± 0.4 , respectively). Haemodynamic parameters were not significantly different from controls.

Conclusion: The abnormality in choroidal perfusion indicated by a reduction in OPA in all LTG patients is unrelated to the presence or absence of vasospasm.

The aetiology of primary open angle glaucomas (POAG) is unknown. Current glaucoma therapy

aims at reducing intraocular pressure (IOP) below 20 mmHg in POAG patients with elevated IOP, and below 15 mmHg in POAG patients with statistically normal IOP (low tension glaucoma, LTG). Even if the goal of this therapy is met, progression of visual field loss and optic nerve head cupping continues in many subjects, mandating that therapeutic concepts independent of reduction of IOP be considered. One of these is ocular blood flow. In other medical fields reduced blood flow is correlated with hypoxic pathologies such as myocardial infarction and stroke. A correlation might also exist for nerve fibre-layer degeneration in glaucoma, especially in those patients who exhibit vasotonus abnormalities.

Gasser *et al.*¹ demonstrated the presence of peripheral vasospasm without any underlying disease by nailfold video-capillaroscopy in 16 patients with a history of cold hands and feet who were also phenomenologically diagnosed as having LTG. Gasser and Flammer² showed an aggravation of visual field defects provoked by cooling one hand of vasospastic patients in cold water. This effect could be reversed by application of the calcium channel blocker nifedipine. Phelps and Corbett³ found that 47% of LTG patients suffered from migraine. Drance *et al.*⁴ showed that 65% of LTG patients without migraine demonstrated a vasospastic reaction determined by finger blood flow measurements.

Quigley *et al.*⁵ did not find a reduction in the number of blood vessels in the optic nerve head region whereas Schwartz⁶ using fluorescein angiography showed filling defects in this area in glaucomatous subjects. These findings suggest a connection between LTG and vascular abnormalities.

The present study was designed to evaluate a parameter of choroidal perfusion, the ocular pulse amplitude (OPA), in LTG patients with respect to vasospasm.

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MATERIALS AND METHODS

Thirty-two LTG patients (14 men, 18 women), 32–56 (mean 43.0) years of age, were selected from a pool of glaucoma patients on the basis of no history of systemic hypertension, diabetes mellitus, elevated cholesterol, neurological deficits, typical migraine headache or smoking and no known eye disease other than the category selected for. The LTG patients chosen had a history of pre-treatment IOPs <21 mmHg, each documented on diurnal curves, had typical glaucomatous visual field loss and disc cupping, and remained on their ocular hypotensive therapy consisting either of epinephrine (1%), pilocarpine (1%) or timolol (0.5%) eye drops, or of epinephrine/pilocarpine or timolol/pilocarpine combinations. The eye drops at the concentrations used in this study have been demonstrated not to affect OPA.^{7,8} The LTG patients were compared with control subgroups selected from a pool of 59 normal non-smoking, non-vasospastic healthy volunteers with no known ocular or systemic disease who showed no visual field defects and/or disc alterations and had IOPs <21 mmHg and who were matched for age (± 3 years), sex, IOP (± 2 mmHg) and refraction (± 1.5 dioptres spherical equivalent).

The study was approved by the appropriate institutional review board and informed consent was obtained from each patient/volunteer following complete explanation of the procedure.

OPA is an indirect measure of choroidal perfusion. A bolus of blood entering the eye corresponding to the cardiac pulse is reflected in a change in IOP as a function of time. The Langham Ocular Blood Flow (OBF) System (OBF Labs, Wiltshire, UK) is a highly sensitive pneumotonometer linked to a data acquisition unit that measures IOP (mmHg) non-invasively with a collection rate of 200 Hz, allowing accurate measurements of OPA with minimal disturbance to

Fig. 1. Ocular pulse amplitudes of low tension glaucoma (LTG) patients (hatched columns) with (LTG-V, $n = 17$) and without (LTG-NV, $n = 15$) a vasospastic reaction, compared with respective matched control subgroups (grey columns). Bars represent mean $\pm$ SEM. * $p < 0.05$ compared with control eye measurements using a two-tailed, unpaired *t*-test.

the eye. OPA may have potential to evaluate some characteristics of OBF in a clinical setting. However, OBF was not calculated from OPA measurements because extraocular factors are involved (e.g. pulse rate, posture) and, in our opinion, the underlying assumptions and the software provided with the OBF system are not adequately documented to calculate the true absolute OBF from the pulse data.

In addition to pneumotonometric values, IOP was measured by Goldmann applanation tonometry. Brachial artery pressures and heart rate (HR) were measured using a blood pressure cuff and a stethoscope. Applanation IOP, blood pressure (BP) and HR were taken before OPA measurements.

A nailfold capillary blood test was performed in all patients/volunteers. A person was considered 'vasospastic' when blood flow cessation in the nailfold capillaries after cold water provocation was >12 s as measured by video-capillaroscopy.⁹ All measurements were taken with the patients and volunteers in supine position.

Statistics

All data represent arithmetic mean $\pm$ standard error of the mean (SEM). Student's unpaired two-tailed *t*-test was used for statistical analysis. Measurements were performed on both eyes of each subject. The level of significance was 5%, i.e. $p < 0.05$ was considered significant. LTG subtypes with vasospasm (LTG-V) and without vasospasm (LTG-NV) were compared with matched subgroups from a pool of healthy volunteers and with each other.

RESULTS

OPA (mmHg) in the LTG patients with a vasospastic reaction (LTG-V, 1.4 ± 0.1 , $n = 17$) was not significantly ($p > 0.09$) different when compared with non-vasospastic LTG patients (LTG-NV, 1.5 ± 0.2 ,

Fig. 2. Intraocular pressures of LTG patients (hatched columns) with (LTG-V, $n = 17$) and without (LTG-NV, $n = 15$) a vasospastic reaction, compared with respective matched control subgroups (grey columns). Bars represent mean $\pm$ SEM. * $p < 0.05$ compared with control eye measurements using a two-tailed, unpaired *t*-test.

Table I. Systemic haemodynamic parameters of low tension glaucoma patients with (LTG-V, *n* = 17) and without a vasospastic reaction (LTG-NV, *n* = 15) and respective control subgroups, showing systolic and diastolic blood pressures (BP) and heart rate

<i>BP systolic (mmHg)</i>	
Control-NV	136.8 ± 5.6
LTG-NV	134.3 ± 8.2
Control-V	134.5 ± 6.9
LTG-V	132.7 ± 7.7
<i>BP diastolic (mmHg)</i>	
Control-NV	82.2 ± 4.2
LTG-NV	78.6 ± 6.5
Control-V	81.0 ± 3.7
LTG-V	79.3 ± 6.3
<i>Heart rate (min⁻¹)</i>	
Control-NV	63.6 ± 3.1
LTG-NV	66.1 ± 3.4
Control-V	63.3 ± 3.4
LTG-V	65.7 ± 3.9

n = 15) but was significantly (*p* < 0.001) reduced in LTG-V and LTG-NV patients when compared with matched healthy control subgroups (2.3 ± 0.2 and 2.4 ± 0.3, respectively) (Fig. 1).

IOP (mmHg) in LTG-V (13.3 ± 0.4) and LTG-NV (13.2 ± 0.5) patient groups was not significantly (*p* > 0.05) different when compared with each other but was significantly (*p* < 0.05) lower when compared with matched healthy control subgroups (15.0 ± 0.3 and 15.2 ± 0.4, respectively) (Fig. 2).

Systolic blood pressure, diastolic blood pressure and HR were not significantly (*p* > 0.05) different when LTG-V and LTG-NV groups were compared with respective matched healthy control subgroups and with each other (Table I).

DISCUSSION

Although approximately half the LTG patients showed a vasospastic reaction (LTG-V), OPA was significantly reduced in all LTG patients and did not correlate with the fingernail capillary vasospastic response to hypothermia. LTG is associated with an ocular vascular abnormality. We interpret the low OPA in both LTG groups as an apparent reduction in choroidal capacity. Similar low OPAs were observed in patients with retinitis pigmentosa¹⁰ and diabetic retinopathy,¹¹ both of which are ocular pathologies where vascular capacity is lost due to vascular degeneration and/or non-patent vessels.

Our findings match those of James and Smith,¹² who demonstrated a reduction in OPA in LTG patients, and those of Kitazawa *et al.*¹³ who demonstrated that half of their LTG and POAG patients with elevated IOP suffered from vasospastic disorders. Flammer¹⁴ has proposed that recurrent vasospasm in the eye may, in some cases, finally lead to structural damage, presenting itself phenomenologically as LTG.

The reduction in OPA in these patients suggests a compromised choroidal circulation which exhibits

impeded functional reserve in the choroid and may reflect a primary decrease in choroidal capacity,^{7,8} decreased perfusion pressures as measured by oculo-oscillo-dynamography,¹⁵ and/or reduced ophthalmic artery perfusion.^{16,17} OPA is an overall measure of choroidal perfusion; thus the optic nerve head circulation, which is an area of circulatory importance in the glaucomas also demonstrating compromised autoregulatory capacity in LTG,¹⁸⁻²¹ can hardly be evaluated with this method. However, the compromise of this vascular structure may increase the relevance of choroidal perfusion in the pathogenesis in LTG. A review of the literature shows contradictory results regarding the role of timolol with respect to ocular circulation. Trew and Smith²² noted no improvement in pulsatile ocular blood flow (POBF) following application of timolol 0.25% in POAG patients, whereas following application of timolol 0.5% Boles Carenini *et al.*²³ showed a significant decrease in POBF; Martin and Rabineau²⁴ noted a reduction in the mean retinal arterial diameter. Following application of pilocarpine 2% and 4% Carenini *et al.*²⁵ noted an increase in POBF.

In our studies the topical glaucoma drugs at the concentrations used in this study reduced IOP but did not affect OPA in ocular hypertensive volunteers.^{7,8} Furthermore, POAG patients on the same drugs demonstrated an OPA similar to a matched healthy control group and significantly increased when compared with LTG patients on the same drugs.^{7,8} This lack of change in OPA may demonstrate a relative negative effect of these drugs on choroidal circulation, since a reduction of IOP which reflects a reduction of the compressive force on the choroid, a low-resistance vascular structure,²⁶ should lead to an increase in OPA. Thus, under the specific conditions of this study, we presume to have measured neither a direct drug-induced nor an indirect (due to the reduction in IOP) change in OPA.

The apparent decrease in choroidal capacity in LTG suggests a vasodilatory approach to the choroid. However, caution is indicated in choosing a vasodilator for improving and not reducing choroidal perfusion – which could occur, for example, by dilation of preocular vessels that induces a redistribution of blood flow away from the eye. An example is isosorbide dinitrate (ISDN), a vasodilator used in the treatment of systemic hypertension and coronary heart disease which reduces systolic ophthalmic artery pressure, systolic ocular perfusion pressure and OPA.²⁷ These changes may indicate a redistribution of blood flow from pulsatile to non-pulsatile, but they could also reflect an overall reduction in ocular perfusion which could further reduce the already compromised choroidal perfusion in these patients. Thus, long-term nitrate therapy

may not favour the ophthalmic circulation. A negative effect on progression of nerve fibre layer degeneration in LTG patients who are on nitrates for other disorders is conceivable.

Nifedipine, a calcium channel blocker, is mainly an arterial vasodilator and systemic antihypertensive agent used in vasospastic diseases. This agent could be beneficial in those LTG patients with vasospastic reaction, but not those who are normal with respect to the fingernail test. Gaspar *et al.*⁸ found an improvement in visual fields by 1.2 dB in 59 patients with visual field defects following application of nifedipine and Kitazawa¹³ demonstrated visual field improvements in 6 of 25 LTG patients following application of the same drug. Lumme *et al.*²⁹ found that nifedipine has no influence on progression of optic nerve head cupping while Netland *et al.*³⁰ observed a significant decrease in the progression of LTG but not in POAG with elevated IOP over a 3.4-year period. These findings could be related to improving the reduced choroidal perfusion in these patients and thus improved nourishment to and removal of potential toxic waste products from the retinal pigment epithelium and the adjacent non-vascularised outer layers of the retina, macula and optic disc regions in LTG patients.

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Key words: Low tension glaucoma, Vasotonus, Choroid, Choroidal perfusion, Ocular pulse amplitude.

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