

EXTENDED REPORT

Value of retinal vein pulsation characteristics in predicting increased optic disc excavation

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Glaucoma is the second commonest cause of blindness in the developed world,¹ and remains the second most important cause of blindness and visual impairment globally.² Its aetiology remains unclear; however, elevated intraocular pressure (IOP) and optic nerve haemorrhage (ONH) are the major risk factors linked to the presence of glaucoma and its progression.³ The optic disc forms a barrier between two pressure compartments: IOP anteriorly and intracranial pressure posteriorly. The central retinal vein passes from the IOP compartment to the intracranial pressure compartment, and can normally be seen to pulsate on the retinal or disc surface. However, such pulsations are known to be absent when intracranial pressure is raised,⁴ and in such situations it has been postulated that ophthalmodynamometric induction of pulsation could allow the non-invasive measurement of intracranial pressure.⁵ Recently, we have shown that pulsation properties of the central and hemiretinal veins are strongly correlated with the presence of glaucoma and its severity.⁶ We wished to explore whether retinal vein pulsation properties have predictive value in determining which patients with glaucoma are more likely to progress.

Glaucoma is an optic neuropathy often associated with raised IOP, with cardinal signs of progressive optic disc neuroretinal rim loss, nerve fibre layer loss and a greater incidence of ONHs. ONHs are significant predictors of progression; however, their aetiology is unknown.^{3,7} Various authors postulate arterial occlusion or venous occlusion as their cause.^{8,9} Additionally, glaucoma is strongly associated with central retinal vein occlusion.¹⁰ Central corneal thickness has recently been shown to be a risk factor for the development of glaucoma,¹¹ but it may not be associated with progression.¹² However, it is known that

Background: Retinal vein pulsation is often absent in glaucoma, but can be induced by applying a graded ophthalmodynamometric force (ODF) to the eye, which is elevated in glaucoma.

Aim: To assess whether ODF has a predictive value in determining glaucoma progression.

Methods: 75 patients with glaucoma and suspected glaucoma were examined prospectively in 1996, and then re-examined at a mean of 82 months later. All subjects had intraocular pressure, visual fields, stereo optic disc photography and ODF measured on their initial visit. When venous pulsation was spontaneous, the ODF was said to be 0 g. At re-examination, central corneal thickness and blood pressure were also measured. Initial and subsequent optic disc photographs were compared and graded into those that had increased excavation and those that had remained stable. The relationship between increased excavation (recorded as a binary response) and the measured variables was modelled using a multiple mixed effects logistic regression.

Results: ODF at the initial visit was strongly predictive of increased excavation ($p=0.004$, odds ratio 1.16/g, range 0–60 g), with greater predictive value in women than in men ($p=0.004$). Visual field mean deviation was predictive of increased excavation ($p=0.044$), as was optic nerve haemorrhage in association with older age ($p=0.038$). Central corneal thickness was not significantly predictive of increased excavation ($p=0.074$) after having adjusted for other variables.

Conclusion: ODF measurement seems to be strongly predictive of the patient's risk for increased optic disc excavation. This suggests that ODF measurement may have predictive value in assessing the likelihood of glaucoma progression.

patients with more severe glaucoma, as indicated by worse visual field loss, are more likely to progress.³

Spontaneous venous pulsation of the central or hemiretinal veins occurs in 98% of elderly normal subjects and in only 54% of patients with glaucoma.⁶ When absent, it can be induced by applying a force with an ophthalmodynamometer.¹³ Generally, the pulsation induced will occur in one or both hemiretinal veins or the central retinal vein. The hemiretinal veins are the two major veins crossing the optic disc margins superiorly and inferiorly to join in the central optic disc. The minimum ophthalmodynamometric force (ODF) required to induce pulsation in one of these vessels is termed the ODF. This ODF is raised in glaucoma,^{14,15} and is associated with glaucoma severity.¹⁶

Physical modelling of blood flow through the eye shows several dominant factors, leading to a requirement of greater ODF for venous pulsation.^{17,18} These factors are an elevated cerebrospinal fluid pressure,^{4,19} increased venous resistance distal to the point of pulsation,¹⁸ lower pulse, to a lesser extent,²⁰ and greater mean blood pressure and a reduced retinal microvascular resistance. Increased cerebrospinal fluid pressure leads to papilloedema and can be excluded by physical examination. The relationship between ODF and glaucoma severity is independent of mean and pulse blood pressure.¹⁶ Microvascular resistance tends to increase in glaucoma,^{21,22} which will tend to reduce ODF.

In order to measure any relationship between ODF and the risk of optic disc excavation, the group of subjects initially

Abbreviations: ODF, ophthalmodynamometric force; ONH, optic nerve haemorrhage; IOP, intraocular pressure

studied in 1996 and 1997^{6, 14} were invited back for review after 6 years. Flicker stereochronoscopy was used to detect increased excavation comparing simultaneous stereo disc photographs using a technique described previously.²³ The precision of our ODF measurements is 21% coefficient of variation with a mean standard deviation of 2.4 g,¹⁶ suggesting that ODF comparison may be valid. We were interested in determining whether an ODF measurement added useful clinical information to the standard management of patients with glaucoma and those with ocular hypertension. In particular, we wished to know whether ODF measurements may have any value in predicting subjects at risk of increasing optic disc excavation.

METHODS

Consecutive eligible patients with glaucoma or suspected glaucoma suspects were examined over an 18-month period by one clinician in 1996 and 1997 for venous pulsation characteristics. All of these subjects were invited back in 2003 for re-examination in order to allow comparison. All of these subjects were being closely monitored, with regular IOP measurements and appropriate therapeutic changes to maintain optimally low IOP as per standard clinical practice. The research followed the tenets of the Declaration of Helsinki, in accordance with the University of Western Australia, Human Ethics Committee; all measurements and photography were taken after informed consent had been obtained from the subjects.

The initial visit measurements have been described previously.^{6, 14} Briefly, patients with glaucoma were defined as subjects with a repeatable Humphrey (Humphrey Systems, Dublin, California, USA) 24-2 full threshold strategy visual field deviation consistent with glaucoma and congruent excavation of the neuroretinal rim. Glaucoma suspects were defined as subjects with a baseline increased IOP >21 mm Hg or with a suspicious appearance to the optic disc, but with normal visual fields on the basis of a normal glaucoma hemifield test on the Humphrey 24-2 full threshold strategy. At least two Humphrey visual field tests were performed, with the second or latter having reliability indices better than 25%. All patients with glaucoma and many of the glaucoma suspects were receiving IOP-lowering treatment.

The pupils were dilated and simultaneous stereo optic disc photographs were taken with a Nidek 3DX camera (Nidek, Gamagori, Japan). Subjects were excluded if significant cataract precluding a clear view of the posterior pole and/or signs consistent with a central or hemiretinal retinal vein occlusion were present. Subjects who developed retinal venous occlusion during the follow-up period were also excluded. The central retinal and hemiretinal veins were examined for spontaneous venous pulsation. If this was present, the ODF was said to be zero for the purposes of data analysis. If absent, then a slit-lamp-mounted ophthalmodynamometer with corneal contact lens (American Optical, Buffalo, New York, USA)²⁴ was used to apply force to the eye while the observer monitored the hemi and central retinal veins for pulsation. The minimum ODF required to induce venous pulsation was recorded. IOP was measured using Goldmann applanation tonometry before ophthalmodynamometry. The Humphrey visual field mean deviation was recorded from the second or latter visual field obtained within 3 months of the initial examination.

At the second examination, the pupils were again dilated, followed by simultaneous stereo disc photography, and central corneal thickness was measured (Quantel, Pocket Pach 2, Clemons, France). We assumed that central corneal thickness would not have changed significantly over the study period.

The stereo disc photographs from left and right eyes from the two visits were deidentified and filed in random sequence.

Mechanical stereochronoscopy was used to compare stereo disc photographs from the two visits.²³ Three independent observers examined all stereo disc photographs and were blinded to the identity of the photographs. Each observer examined optic discs for the presence or absence of a disc rim haemorrhage and for loss of neuroretinal rim. The location of the neuroretinal rim change was documented as being the nasal, superior, temporal or inferior quadrants. Increased excavation (recorded as a binary "yes or no" variable) was said to occur when all three observers noted loss of neuroretinal rim in the same location. Where one or two out of the three observers noted a change, the stereo photographs were reviewed together at a consensus meeting and a decision made as to whether a change had occurred. Similarly, ONH was said to occur when all three observers agreed or when consensus was reached regarding observation of the initial disc photographs.

Statistical analysis

Mean and standard deviations were calculated and are reported for the key data. Student's *t* test was used to compare means. We modelled excavation (yes or no) against initial IOP, initial ODF, initial mean deviation, central corneal thickness, age, sex and presence of ONH. We also considered interaction terms between the binary variables (disc haemorrhage status and sex) and the quantitative explanatory variables.

The analysis used a logistic regression model based on data from both eyes, including a random effect to account for the inter-eye correlation within subjects.²⁵ This type of model is a generalised linear mixed model, and can be fitted using penalised quasi-likelihood.^{26, 27} All variables and interactions listed above were included in the initial generalised linear mixed model. Backwards variable selection was then implemented using Wald *t* tests, with $p > 0.1$ as a criterion for variable removal. The statistical principle of marginality (whereby interactions must always be accompanied by corresponding main effects) was respected. All calculations were performed using the statistics software package R.²⁸

RESULTS

Out of the 199 subjects seen at the first visit, 115 subjects were re-examined at a mean (SD) of 82 (7.3) months after the first visit. Of those subjects examined, full datasets were obtained from 136 eyes of 75 subjects. The mean (SD) age was 68 (12.2) years at the final visit. In all, 36 were women (mean age 68.7 (11.0) years) and 39 were men (mean age 67.3 (13.3) years). The mean central corneal thickness was 531 μ m, with the subjects having an average mean deviation of -6.5 dB. No significant difference was found between the sexes in any of these parameters using Student's *t* test. A total of 60 eyes had glaucoma and 76 were glaucoma suspects. The mean (SD) defect was -6.0 (6.7) dB: -9.7 (7.7) dB for glaucoma eyes and -2.4 (2.0) dB for suspects. Mean (SD) IOP was 21.1 (6.1) mm Hg: -19.5 (6.2) mm Hg for glaucoma eyes and 22.6 (5.6) mm Hg for suspects. Of the patients with glaucoma, 56 had primary open-angle glaucoma and four had pigment dispersion syndrome. Similar proportions showed increased excavation in each group ($\chi^2 = 0.036$, $p = 0.85$), with 11 out of the 60 glaucoma eyes and 14 out of 76 suspect eyes having increased excavation. In all, 43 subjects had no spontaneous venous pulsation at the initial visit, with a mean ODF of 13.4 (SD 13.1, range 1-60) g. No optic disc swelling or papilloedema was seen at any visit. A total of 13 female eyes out of 67 and 12 male eyes out of 69 progressed. In all, 28% of eyes without spontaneous venous pulsation had increased excavation compared with 14% of eyes with spontaneous venous pulsation.

Table 1 Predictive model: mixed effects logistic regression with listed variables predicting increased excavation

Variable	Value	SE	p Value
Intercept	5.57	4.45	0.214
MD	-0.100	0.049	0.044
ODF	0.150	0.050	0.004
Age	-0.149	0.069	0.035
SexM	-12.3	5.8	0.036
ONH	-17.0	10.0	0.095
ODF:sexM	-0.200	0.067	0.004
Age:sexM	0.200	0.085	0.022
Age:ONH	0.306	0.144	0.038

ODF, ophthalmodynamometric force; ONH, optic nerve haemorrhage; MD, visual field mean deviation. Only significant variables at a 5% level are shown. Mean deviation is the visual field mean deviation, ODF was taken at the initial visit. Binary variables: sexM was 1 for males and 0 for females; ONH was 1 for haemorrhage and 0 for no haemorrhage.

Our mixed effects logistic regression analysis examined the influence of ODF and other variables on increased excavation. The IOP during the initial visit and the time interval between visits were not associated with increased excavation ($p > 0.4$ for all). ODF was found to be highly predictive ($p = 0.004$, relative risk 1.16/g) of increased excavation after adjustment for mean field defect, age, disc haemorrhage status and sex, as well as IOP and time interval. There was a strong interaction with sex ($p = 0.004$, adjusted for other variables as above), such that this predictive effect of ODF was greater for women than for men. ONH was seen to be a significant predictor of increased excavation in association with age ($p = 0.0382$)—that is, the greater the age at haemorrhage, the more likely that progression would occur. Mean defect was found to be a significant predictor of increased excavation ($p = 0.044$), again after adjustment for other variables. There was a complex relationship between age and increased excavation, with increasing age being predictive of progression for men and for those with disc haemorrhage (table 1). After adjustment for other variables, the effect of corneal thickness did not reach formal statistical significance at the 5% level ($p = 0.074$).

DISCUSSION

The force required to induce venous pulsation was highly predictive of increased excavation even when adjusting for IOP and the other measured variables. Greater ODF leads to a greater odds ratio of 16% for increased excavation (with 95% CI of 10.4% to 22.1%) per gram ODF, adjusted for age and disc haemorrhage status. We cannot explain why the predictive value of ODF was greater for women than for men ($p = 0.004$). It is known that women are more likely to develop glaucoma presenting with IOP in the normal range (normal tension glaucoma), and that this is more likely to progress in women.²⁹ ONHs are more common in women, in those with normal tension glaucoma and in older patients.^{30 31} We did calculate the potential association between ONH and ODF, but found no significant relationship among our data. However, only nine disc rim haemorrhages were seen in our subjects at their initial visit, seven of which were in women. Unfortunately, the low number of subjects with ONH limits the power of this analysis.

In the setting of glaucoma or glaucoma suspects without raised intracranial pressure (no papilloedema), raised ODF probably represents an increased hemi or central retinal vein resistance.¹⁶ ODF is known to be increased in central retinal vein occlusion, and has been used to monitor resolution of central retinal vein occlusion³²; however, subjects with central retinal vein occlusion were excluded from this study. We postulate that, over time, the increased pressure gradient across the optic disc in patients with glaucoma alters central retinal vein haemodynamics, leading to endothelial changes, an increase in venous resistance and a

greater ODF. A high or increasing venous resistance may alter the tributary venule drainage from the optic disc tissue, leading to ischaemic changes. Such changes may aggravate glaucomatous optic neuropathy.

ONH was also a predictor strongly associated with age, such that the likelihood of progression increased the older the age at the time of haemorrhage. It is worth noting that ONHs are more common with increasing age.³⁰ The postulated venular changes may lead to occlusion and disc rim haemorrhage; however, at present, our data lack power and do not lend strong support to this hypothesis.

An interesting relationship was found between age and increased excavation, with increasing age being predictive of increased excavation for men and for those with disc haemorrhage. It is known that age is not associated with progression in women with normal tension glaucoma, raising the possibility that this uncharacterised aspect of glaucoma pathology might have influenced our results.²⁹

Central corneal thickness was not significantly associated with progression ($p = 0.074$) after adjusting for other variables. It should be borne in mind that corneal thickness was measured at the second visit and hence was not a true predictor; however, we assumed that corneal thickness changes little over 8 years.

The judgement of glaucoma progression is usually made after the observation of increased optic disc excavation or visual field worsening. We have used only one of these criteria, but it is generally accepted that increased optic disc excavation implies glaucoma progression.³³ Hence, an increased ODF is likely to be associated with progression in patients with glaucoma and suspects, and its measurement may be a useful clinical tool.

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