Correlation between the orbital and intraocular portions of the optic nerve in glaucomatous and ocular hypertensive eyes

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CLINICAL STUDY

Abstract

Background/Purpose **It has recently been reported that the retrobulbar optic nerve diameter (OND) and cross-sectional area (ONCSA) are reduced in glaucoma. This study was performed to investigate the correlation between the orbital and intraocular portions of the optic nerve.**

Methods **One eye of 20 volunteers (16 glaucoma subjects, 4 ocular hypertension subjects) underwent optic disc analysis using Heidelberg retinal tomography, and echographic measurements of the retrobulbar optic nerve.**

Results **The male-to-female ratio was 6.5:3.5, and the mean age of our sample (± SD) was 62.25 ± 13.7 years. Orbital optic nerve diameter and cross-sectional area correlated significantly and positively with the neuroretinal rim area (Spearman's rank correlation coefficient; OND: $r_S = 0.488$, $p = 0.0336$; ONCSA: $r_S = 0.619$, $p = 0.0079$), but not with any other topographical disc data. The retrobulbar optic nerve cross-sectional area-to-disc area ratio (ONCSA/D) was found to have a significant negative correlation with the cup area/disc area ratio (simple regression analysis; $r = -3.948$, $p = 0.046$), and a statistically demonstrable positive correlation with the neuroretinal rim area/disc area ratio ($r = 0.451$, $p = 0.046$).**

Conclusion **The results of this study indicate that orbital optic nerve dimensions are a reflection of the neuroretinal rim area of the optic disc. Echographic measurements of the retrobulbar nerve may be additive to the traditional triad of raised intraocular pressure, field defects and glaucomatous optic neuropathy that suggests a diagnosis of glaucoma.**

Key words Glaucoma, Optic nerve, Retinal nerve fibre layer, Retrobulbar

Visual impairment related to glaucomatous damage is attributed to retinal nerve fibre loss.[1–5] This axonal loss, in combination with changes in the extracellular matrix of the lamina cribrosa, results in a characteristic form of optic neuropathy.[6–12] Two recent papers have shown that retrobulbar optic nerve thickness is reduced in glaucoma, and have suggested that this too is the result of destruction of the retinal nerve fibre layer (RNFL).[13,14] We performed this study to investigate the relationship between orbital optic nerve dimensions and optic nerve head topographical measurements.

Materials and methods

Twenty patients attending the glaucoma department of the Birmingham and Midland Eye Centre were recruited into the study. Of these, 16 suffered from primary open angle glaucoma and the remainder had a diagnosis of ocular hypertension. The only inclusion criteria were clear optic media and a visual acuity of 6/9 or better. In each case, glaucoma was diagnosed in the presence of raised intraocular pressure (>21 mmHg), field loss and glaucomatous optic disc changes. The criteria for visual field abnormalities included a corrected pattern standard deviation with $p < 0.05$, or a glaucoma hemifield test outside normal limits, obtained with at least two reliable and reproducible visual field examinations using the Humphrey Field Analyzer (program 24–2). The term ocular hypertension (OHT) was reserved for those cases where intraocular pressure was $\geq$ 24 mmHg on at least two separate occasions in an eye with normal optic disc morphometry and no detectable field defect on standard automated perimetry. Subjects were informed of the nature of the study and consent was obtained.

One randomly selected eye of each subject underwent optic disc morphometry (performed with the Heidelberg Retinal Tomograph, HRT)

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and echographic orbital optic nerve measurements (performed with Biovision B-Scan ultrasound). For all measurements, five repeated readings were taken and the mean calculated. There was one operator only for each instrument (S.B., HRT; P.A.G., ultrasound), and HRT was performed before echography in all cases.

We used Spearman's rho (r_S) as the index of correlation between retrobulbar optic nerve dimensions and optic nerve head topographical data. This rank correlation coefficient is required because of the considerable inter-individual variability in orbital optic nerve fibre count.[15] Simple regression analysis was performed to investigate the relationship between numerical data corrected for inter-individual variability of disc size. Reproducibility of the five ultrasonographic measurements of the optic nerve diameter and cross-sectional area was expressed in terms of the coefficient of repeatability. This represents the value below which the difference between two measurements will lie with probability 0.95 and is given by:

$$\text{Coefficient of repeatability} = 2 \times \sqrt{2\,\overline{SD^2}}$$

Instrumentation

Scanning laser tomography

The Heidelberg Retinal Tomograph (HRT; Heidelberg (Germany) Engineering) images the retina in three dimensions and therefore provides topographic measurements. This is achieved by the projection of a diode laser beam (670 nm) via a confocal system. The confocal system ensures that only light reflected from a defined focal plane, which the HRT places on the retina, is detected by the integrated photomultiplier.

To obtain three-dimensional measurements, the HRT acquires 32 equally spaced confocal images along the *z*-axis (perpendicular to the optical axis). The image resolution is 256 × 256 pixels, resulting in 65 536 measurements per image. The operator defines the depth of the scanning range, which can be raised from 0.5 mm to 4 mm. The scanned field size can also be raised (10° × 10°, 15° × 15° or 20° × 20°). Reflectivity along the *z*-axis is used to generate a topographic image, measured in micrometres from the main focal plane.

To allow three-dimensional measurements of the disc, the margin of the optic nerve head is delineated. The calculation of the morphometric parameters is not influenced by the operator (i.e. the HRT automatically computes these data for the entire nerve head on advice), and the height values of the contour line are corrected for the influence of crossing vessels by an automatic interpolation. An additional reference surface plane, to which all fundus elevations and depressions are related, is then defined to allow the depth-located data to be retrieved.

We obtained five independent 10° × 10° images for each eye, centred on the optic nerve head. The pupil was not dilated in any case, and keratometry readings were used to correct for magnification. After each acquisition, the instrument verified that exposure was correct; images of inadequate quality were automatically discarded by the HRT device.

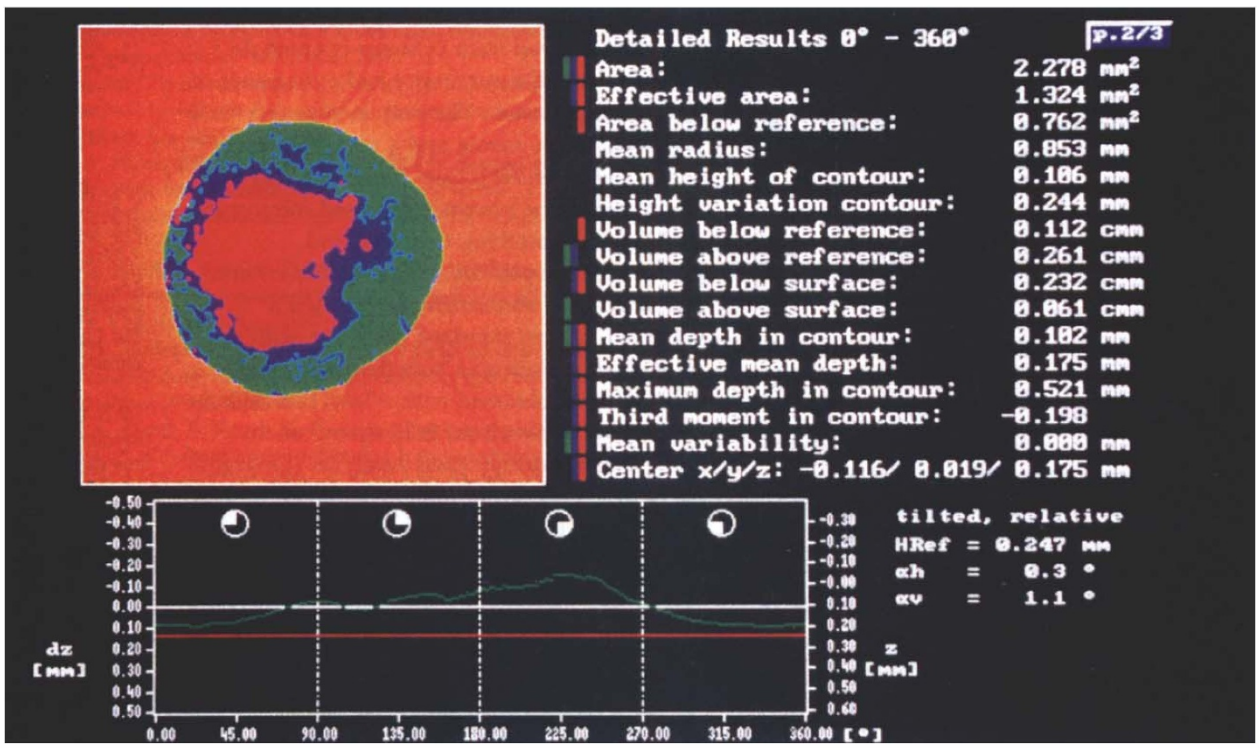

Fig. 1. *Detailed colour-coded results of optic nerve head analysis by the Heidelberg Retinal Tomograph, as displayed on the monitor. All measures of fundus elevations and depressions are made with respect to the reference plane.*

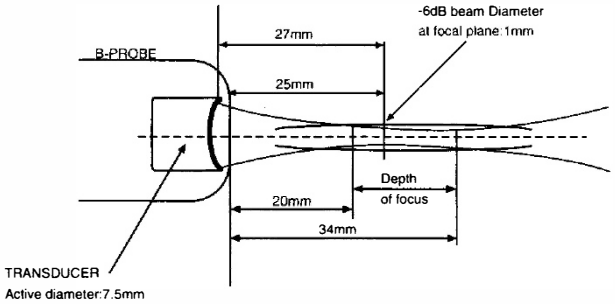

Fig. 2. *Diagrammatic representation of the B-scan probe. The radius of concavity of the transducer is approximately equal to its focal distance (27 mm). As the transducer is 2 mm inside the probe, this ensures an external focus of 25 mm.*

The images were stored in a file on the hard disc drive of the instrument and the following parameters computed: disc area, cup area, cup/disc area ratio, rim area, cup volume, rim volume, mean cup depth, maximum cup depth, mean retinal nerve fibre layer (RNFL) thickness and RNFL cross-sectional area (Fig. 1). The mean of the five values for each parameter was then calculated.

Ultrasound

Retrobulbar optic nerve diameter was measured using standardised, high-resolution B-scan and A-scan echography (Biovision B-Scan, Chiron Vision, UK). The ultrasound probe is focused at 27 mm from the concave transducer (i.e. 25 mm inside the eye), resulting in greater resolution of orbital structures than was achievable by its predecessors. This probe has a lateral resolution of <0.8 mm within the depth of focus (20–34 mm) and achieves lateral and axial resolutions at the focal plane of 0.3 mm and 0.12 mm respectively (Fig. 2).

The technique we used is similar to that described in the literature.[16,17] Briefly, the patient was asked to move his/her eyes in all four positions of gaze for a period of 3 min to induce a redistribution of subarachnoid fluid. The ultrasound probe was then placed on the temporal bulbar conjunctiva with the eye in the primary position. On the echographic screen a transverse B-scan of the orbital optic nerve could be seen, and confirmed by visualisation of the dural echoes on a superimposed A-scan. Optic nerve diameter (OND) was calculated as the maximal inter-pial distance in the horizontal plane. The perimeter of the optic nerve was then delineated

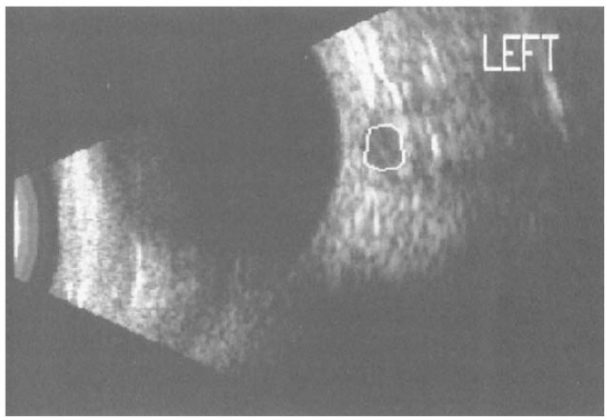

Fig. 3. *The optic nerve cross-sectional area is calculated by the instrument as the area enclosed by the dural sheath, which is marked with a cursor by the operator.*

with the aid of a cursor, and the area within this was calculated by the instrument as the optic nerve cross-sectional area (ONCSA) (Fig. 3). The reproducibility of this technique has been established, and is reported elsewhere.[14]

Some investigators have found the optic nerve to be of uniform thickness throughout its orbital course,[18] whereas others have reported a maximal optic nerve sheath diameter 3 mm behind the eye.[19] In order to minimise inter-subject variability, we took all our echographic readings 2–4 mm posterior to the globe. Each measurement was the mean of five readings taken by one experienced ultrasonographer (P.A.G.) in a masked fashion.

Results

Twenty volunteers (16 glaucoma subjects, 4 OHT subjects) were recruited into this study. Of these, 13 were male. The mean age of our sample (± SD) was 62.25 ± 13.7 years. The mean ± SD refractive error (spherical equivalent) was 0.97 ± 0.959 dioptres (D) (range: −2.0 D to +2.25D) and the mean radius of corneal curvature ranged from 7.23 to 8.030 mm (mean 7.744 mm).

The areas (mean ± SD) of the optic disc and neuroretinal rim were 1.907 ± 0.336 mm^2 (range: 1.149 to 2.432 mm^2) and 1.035 ± 0.232 mm^2 (range: 0.621 to 1.639 mm^2) respectively. The other topographic measurements of the optic nerve head, as measured by the HRT, are given in Table 1.

Table 1. *Topographic measurements of the optic nerve head as measured by the Heidelberg Retinal Tomograph*

	Cup/disc ratio	Neuroretinal rim area (mm^2)	Cup volume (mm^3)	Rim volume (mm^3)	Mean cup depth (mm)
Mean	0.44	1.035	0.252	0.239	0.308
SD	0.136	0.232	0.197	0.106	0.114
Range	0.222–0.716	0.621–1.638	0.012–0.769	0.076–0.484	0.092–0.557
	Max. cup depth (mm)	Cup shape measure	Height variation (mm)	RNFL CSA (mm^2)	Mean RNFL thickness (mm)
Mean	0.696	−0.09	0.374	1.004	0.207
SD	0.204	0.086	0.097	0.276	0.057
Range	0.243–1.053	−0.243–0.072	0.183–0.651	0.563–1.642	0.102–1.642

RNFL, retinal nerve fibre layer; CSA, cross-sectional area.

Table 2. *Echographic measurements of retrobulbar optic nerve diameter and cross-sectional area, and their correlation with optic nerve head topographical data*

	Orbital optic nerve diameter (mean: 2.63 mm; range: 1.96–3.65 mm)		Orbital optic nerve cross-sectional area (mean: 8.1 mm^2; range: 4.92–15.4 mm^2)	
	Spearman's 'rho'	*p* value	Spearman's 'rho'	*p* value
Cup area	0.048	0.83	0.126	0.5819
C/D area ratio	−0.084	0.7148	−0.113	0.6218
Rim area	0.488	0.0336	0.619	0.0079
Cup volume	0.033	0.884	0.132	0.5652
Rim volume	0.183	0.4248	0.236	0.3034
Mean cup depth	−0.033	0.884	0.09	0.6941
Max. cup depth	0.051	0.8249	0.103	0.6523
Cup shape measure	−0.296	0.1972	−0.209	0.3622
Height var. contour	−0.2223	0.3312	−0.332	0.1475
RNFL CSA	0.183	0.4248	0.235	0.3065
Mean RNFL thickness	0.161	0.4821	0.191	0.4052

C/D, cup/disc; RNFL, retinal nerve fibre layer; CSA, cross-sectional area.

Echographic measurements of orbital OND ranged from 1.96 to 3.65 mm, with a mean (± SD) of 2.627 ± 0.418 mm. The standard deviations of the five ultrasonographic readings comprising each measurement ranged from 0.014 mm to 0.241 mm and the coefficient of repeatability was 0.384 mm. OND was positively correlated with neuroretinal rim area (r_S = 0.488, p = 0.0336) but unrelated to other optic disc tomographic data (Table 2).

The mean retrobulbar ONCSA (± SD) was 8.097 ± 2.531 mm^2, with a range of 4.92 to 15.4 mm^2. The standard deviations of the five ultrasonographic readings comprising each measurement ranged from 0.058 mm^2 to 0.379 mm^2, and the coefficient of repeatability was 0.54 mm^2. ONCSA correlated significantly and positively with the neuroretinal rim area of the optic nerve head (r_S = 0.619, p = 0.0079) but not with any other optic disc parameters (Table 2).

The neuroretinal rim area/disc area ratio (NR/D) ranged from 0.284 to 0.788, with a mean ± SD of 0.556 ± 0.136. The NR/D was found to have a significant positive correlation with the neuroretinal rim volume (simple regression analysis; r = 0.853, p = 0.013), and a significant negative correlation with cup area (r −0.344, p < 0.001), cup volume (r = −0.563, p = <0.0001), cup shape measure (r = −1.16, p = 0.0002) and mean cup depth (r = −0.805, p = 0.001). There was no statistically demonstrable relationship between the NR/D and other topographical disc data (r = 0.12–0.94, p = 0.056–0.29).

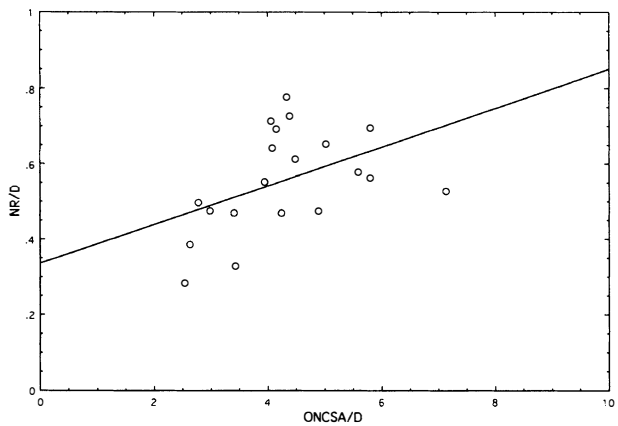

Fig. 4. *Simple regression scattergram of the orbital optic nerve cross-sectional area/disc area ratio (ONCSA/D) versus neuroretinal rim area/disc area ratio (NR/D).*

The mean (± SD) optic nerve cross-sectional area/disc area ratio (ONCSA/D) was 4.285 ± 1.189 (range: 2.541–7.135). The ONCSA/D was found to have a significant negative correlation with the cup/disc ratio (simple regression analysis; r = −3.948, p = 0.0463). No other HRT data were found to be related to the ONCSA/D in a statistically meaningful way (r = −4.1 to 3.4; p = 0.07 to 0.86).

There was a statistically demonstrable positive correlation between ONCSA/D and NR/D (r = 0.451, p = 0.046) (Fig. 4).

Discussion

The ophthalmic assessment of the glaucoma suspect is based on the results of visual field testing, tonometry and evaluation of the optic nerve head.[20] However, the usefulness of intraocular pressure (IOP) measurements is limited as raised IOP is neither sufficient nor necessary to arrive at a diagnosis of glaucoma.[21–24] Furthermore, reproducible field defects only become apparent 6 years following demonstrable RNFL loss in 60% of glaucoma patients,[5] and in many cases satisfactory perimetry is precluded by the physical or mental limitations of the patient. Consequently, in the absence of expensive specialist equipment, clinical evaluation of the optic nerve head may be the only indicator of glaucomatous damage in many subjects.

Glaucomatous optic neuropathy is well described,[25] and is characterised by loss of the neuroretinal rim,[26] notching of the rim, bayoneting and nasal deviation of the disc vessels,[25] and interocular asymmetry of the cup/disc ratio.[27] Loss of retinal nerve fibres has been demonstrated in glaucoma,[28,29] and the RNFL disturbances correlate well with the extent of pathological optic disc cupping.[1,2,4,6] Since the RNFL contains the retinal ganglion cells and is part of the optic nerve, a reduction in the size of retrobulbar nerve might be expected in glaucoma. This has been investigated, and confirmed, by us and by other workers.[13,14] However, the

correlation between orbital optic nerve dimensions and optic nerve head morphology, as measured by the HRT, has not previously been investigated.

We have shown that the orbital optic nerve diameter and cross-sectional area correlate positively and significantly with neuroretinal rim area, but not with any other optic nerve head topographical data. This is consistent with the findings of Dichtl and Jonas,[13] who also demonstrated decreasing optic nerve thickness with decreasing neuroretinal rim area. However, several differences between the two studies in terms of methodology warrant mention. First, we used new-generation ultrasonography with much greater image resolution of structures in the retrobulbar region because of its posteriorly placed focus, and we combined A-scan and B-scan echography thus reducing the possibility of artefactual error. Second, we measured optic nerve diameter and cross-sectional area and investigated the relationship of both these parameters with morphometric data of the optic disc. Finally, optic nerve head analysis was performed using the HRT in the present study, whereas Dichtl and Jonas used magnified colour stereo photographs.[13] The accuracy of the HRT has been established, and its relative error has been estimated to be 0.3–3.1% for cup diameter, 2% for cup area and 11.7% for cup depth measurements when verified against a model eye.[30,31] Furthermore, topographical measurements of the optic nerve head using confocal laser scanning devices and planimetric measurements of colour stereoscopic optic disc photographs have been shown to differ significantly.[32,33]

Although the optic nerve fibre count has been shown to correlate significantly and positively with the orbital optic nerve cross-sectional area,[34,35] the role of measurements of the retrobulbar optic nerve in glaucoma assessment may be limited because of the considerable inter-individual variability in its dimensions.[15] Optic disc area correlates significantly and positively with neuroretinal rim area,[36] and has been shown to reflect optic nerve fibre count[37] and retinal photoreceptor count.[38] However, in contrast with the neuroretinal rim area and the orbital optic nerve cross-sectional area, the disc area is unaffected by axonal loss. These disc properties have resulted in its use as the most commonly employed optic nerve head parameter against which the cup size is measured. The cup/disc (C/D) ratio enlarges with progression of glaucomatous damage, reflecting loss of optic nerve fibres which are represented in the optic disc by the neuroretinal rim.[25] Furthermore, several investigators have shown that larger, non-glaucomatous, discs have larger C/D ratios,[39,40] and that glaucomatos optic neuropathy is more difficult to detect in small discs.[40,41] Also, it has been suggested that eyes with larger discs and orbital optic nerves have greater anatomical reserve capacity and are less susceptible to glaucomatous damage.[36,38] In order to adjust for the inter-individual variability in the pattern and behaviour of different optic discs, we incorporated the orbital optic nerve cross-sectional area into a ratio with its corresponding optic nerve head area and named this the ONCSA/D ratio. If the retrobulbar optic nerve does reflect the neuroretinal rim area it will have a demonstrable significant and positive correlation with the neuroretinal rim area-to-disc area (NR/D) ratio, and a significantly negative correlation with the C/D ratio. Furthermore, one would expect the ONCSA/D and the NR/D to be more sensitive indicators of axonal loss, as each ratio is an expression of the current optic nerve fibre count as a fraction of the baseline count for that individual eye. This is confirmed by our findings that showed the ONCSA/D and the NR/D to be significantly and positively correlated, whereas a significant inverse relationship existed between the ONCSA/D and the C/D ratios.

The orbital optic nerve lies between the globe and the optic foramen, and is between 20 and 30 mm long. It is considerably wider (3–4 mm) than its intrascleral portion due to the addition of myelin sheaths.[42,43] Histologically, the retrobulbar nerve is arranged in fascicles of axons surrounded by extra-fascicular matrix.[44] The collagen types in the matrix of the retrobulbar nerve are similar to those found at the lamina cribrosa.[44]

At a microscopic level, approximately 50% of the lamina cribrosa is occupied by nerve fibres, and 50% by extracellular matrix (ECM).[45] The core of the cribriform plates forming the lamina cribrosa is made up of elastic fibres and collagen, and the plates themselves are coated with collagen type IV and laminin.[46] The mechanical properties of these macromolecules of the ECM are thought to render the lamina cribrosa compliant, and resilient to fluctuations in IOP.[46]

The development of glaucomatous optic neuropathy is attributed to loss of ganglion cell axons[6–9] in association with alterations in the connective tissue of the lamina cribrosa.[10–12] In chronic open angle glaucoma, which is primarily a disease of the elderly, increasing rigidity of the laminar ECM with age has been implicated in this process. However, there is no consensus on whether this loss of flexibility and resiliency by the lamina cribrosa is a consequence of raised IOP, axonal loss or the ageing process alone.[47] Increasing age is associated with axonal loss in the retrobulbar optic nerve, but its effect on the ECM of the orbital nerve has yet to be established.

We were uncertain at the outset of this study, therefore, whether the extent of neuroretinal rim loss would be reflected in altered retrobulbar optic nerve size. Our findings of a significant and positive relationship between the orbital optic nerve cross-sectional area and the neuroretinal rim area, and the ONCSA/D and NR/D, indicate that changes in the size of the retrolaminar optic nerve are an indication of glaucomatous damage and axonal loss.

It is worth noting, however, that we did not find the orbital optic nerve diameter and cross-sectional area to be significantly related to the retinal nerve fibre layer thickness or cross-sectional area, and that this contrasts with the findings of one previous study where RNFL thickness was assessed using wide-angle red-free fundus photographs.[13] Our findings suggest that the reduced

retrobulbar optic nerve dimensions in glaucoma are not the result of diminished optic nerve fibre count alone, but also of associated and simultaneous changes in the extrafascicular matrix of the orbital nerve.

We have mentioned the limited contribution IOP measurements can make to the assessment of the glaucoma suspect and the problems associated with visual field analysis in the detection of early glaucomatous damage. However, the role of optic nerve head morphometry may also be restricted. Clinical evaluation of the optic disc may be impossible where media opacities exist, or difficult to interpret in the presence of small or tilted discs.[40,41] Under such circumstances, echographic measurements of the orbital optic nerve could be additive to the clinical assessment. Optic nerve diameters below 2.25 mm, and optic nerve cross-sectional areas less than 4.9 mm^2, should be considered pathologically reduced and regarded with suspicion.[14] Furthermore, interocular asymmetry of retrobulbar optic nerve dimensions is also suggestive of glaucoma.[14,19] Finally, as ultrasonographic imaging techniques improve there may be a role in the future for serial measurements of the orbital optic nerve as a means of monitoring glaucoma.

In conclusion, we have shown that the retrobulbar optic nerve dimensions correlate significantly and positively with the neuroretinal rim area. Orbital optic nerve echography can be a useful tool in the clinical assessment of the glaucoma suspect, and may be contributory in those cases where the traditional triad of tonometry, optic nerve head morphometry and field analysis fails to establish a diagnosis.

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