Peripapillary retinal blood flow in normal tension glaucoma

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Abstract

Aims—To determine if normal tension glaucoma (NTG) patients differ from age matched controls in blood flow to the peripapillary retina, as measured with confocal scanning laser Doppler flowmetry (cSLDF; “Heidelberg retinal flowmetry”).

Methods—12 NTG patients and 12 age matched controls were compared using (a) 10×10 pixel boxes (the instrument default sample size), taken from the nasal and temporal peripapillary retina, (b) the average from two of these boxes, and (c) every qualifying pixel within the peripapillary retina.

Results—Patients and controls did not differ in blood flow measured using the default sample from a single 10×10 pixel box, placed in either the temporal or nasal peripapillary retina, or expressed as the average from these two boxes. However, in histograms using every pixel from the peripapillary retina, NTG patients displayed significantly higher percentages of minimal flow pixels (defined as less than one arbitrary unit of flow: 30% v 19%, p<0.01), and significantly lower flow in the 25th, 50th, and 75th percentile flow pixel (each p<0.05) than did age matched controls.

Conclusion—NTG is characterised by reduced blood flow in the peripapillary retina, a result suggesting that blood flow deficits accompany, and perhaps may contribute to, disease development in these patients.

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Glaucoma may result from the programmed death of retinal ganglion cells,1,2 as initiated by complex factors that include mechanical compression and ischaemia.3 Seen in these terms, it is apparent that defining the level of blood flow in and around the optic nerve head is an important goal for visual science—to test hypotheses regarding blood flow and disease, to determine disease severity, and to monitor treatment interventions.

Several lines of evidence suggest that patients with normal tension glaucoma (NTG) may suffer from ocular blood flow deficits. In these people, vascular resistance downstream from the central retinal and posterior ciliary arteries is increased,4,5 choroidal filling times are prolonged,5 areas of indocyanine green hypofluorescence are increased in the peripapillary region,6 and diffuse ischaemia may exist throughout the brain.7 However, these haemodynamic markers provide no direct information about perfusion of the retina or optic nerve head. In this study, confocal scanning laser Doppler flowmetry (cSLDF) was used to determine capillary blood flow in the peripapillary retina near the optic nerve head.8 Previous studies that have used this technique have failed to detect a perfusion difference between controls and patients with NTG.9,10 However, those experiments utilised the default 10×10 pixel sampling box, a method that exhibits a high coefficient of variation when repeated on a weekly basis.11 In this study, in addition to conventional analysis, we utilised a new methodology that includes every qualifying pixel within the entire cSLDF image.12 Besides measuring the distribution of low and high flow pixels within the sample, this novel method reduces the coefficient of variation of repeated measurements by nearly 50%.12

Patients and methods

SUBJECTS

Twelve patients (seven women, five men; mean age 54 (SD 3) years) and 12 age and sex matched controls with normal eye examinations (eight women, four men; mean age 49 (3) years) were recruited for study. A homogeneous group of patients with early stage normal tension glaucoma were recruited from the Indiana University Hospital Glaucoma Service. All patients had either substantial optic disc cupping (C/D ratio >0.8), or a combination of less severe cupping (C/D ratio 0.6 to 0.7) and visual field defects measured as either mean deviation (MD) or corrected pattern standard deviation (CPSD). For the group of 12 patients, C/D ratio averaged 0.7 (SD 0.1), MD averaged 4.2 (4.9) dB, and CPSD averaged 6.37 (5.44) for the central 24-2 of Humphrey automated perimetry. All subjects had intraocular pressure less than 21 mm Hg (mean IOP 16 (2) mm Hg), with normal diurnal curve measurements. Gonioscopy indicated open anterior chamber angles in all patients, and none had a history of orbital or ocular trauma. Both patients and controls were free from any history of hypertension or diabetes. Before participating, subjects signed informed consent to procedures reviewed and approved by an institutional review board. All experimental procedures conformed to the tenets of the Declaration of Helsinki.

EXPERIMENTAL DESIGN

Patients and controls were each studied on a single occasion. The eye with the more severe visual field defect was chosen in patients; the right eye was examined in controls. Patients ceased all ocular and systemic medications for 3 weeks before study.
Table 2  Pixel by pixel flow analysis in normal tension glaucoma (NTG) patients and controls

<table>
<thead>
<tr>
<th>Aspect of analysis</th>
<th>NTG</th>
<th>Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal flow (% of total pixels)</td>
<td>30.0 (3.3)</td>
<td>18.5 (1.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>Flow in selected pixels (arbitrary units)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25th percentile</td>
<td>183 (38)</td>
<td>324 (27)</td>
<td>0.007</td>
</tr>
<tr>
<td>50th percentile</td>
<td>446 (64)</td>
<td>636 (50)</td>
<td>0.03</td>
</tr>
<tr>
<td>75th percentile</td>
<td>751 (100)</td>
<td>1017 (89)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Analysis from the entire image

When flow histograms are generated from the entire image, flow is recorded for every pixel within the 256 × 64 pixel image. Figure 1 shows the 1 × 1 pixel sampling window. After elimination of pixels that contain major vessels, are poorly focused, or are improperly illuminated, the remaining values are sorted on the basis of flow. As with the 10 × 10 pixel box, the flow in the pixel at 25th, 50th, 75th, and 90th percentile is determined.

Statistical analysis

Comparisons of values obtained from patients and controls were made using two tailed unpaired t-tests, with p <0.05 regarded as significant.

Results

Patients’ controls: default small box analysis

Patients and controls did not differ in cSLDF measurements of blood flow using the default 10 × 10 pixel box in either the temporal or nasal peripapillary retina. In addition, the two groups did not differ in flow when values obtained from these two areas were averaged. Group mean values for blood flow, as measured at each site, and the average from the two sites, are shown in Table 1.

Patients’ controls: entire image analysis

Approximately 1200 pixels, obtained from the entire peripapillary retinal image, were included for an average subject in this phase of the study. This number, which did not differ between patients and controls, represents a sample size approximately 12-fold greater than that obtained from the default 10 × 10 pixel box. The percentage of these qualifying pixels that contained minimal flow was significantly increased in NTG patients (Table 2). In addition, flow in the pixels at the 25th, 50th, and
75th percentile of flow were significantly reduced in the patients as compared with controls (Table 2).

Discussion

In this study we found reduced peripapillary capillary flow in normal tension glaucoma (NTG) patients compared with age matched controls, using analysis of the entire confocal scanning laser Doppler flowmeter (cSLDF) image. These reductions presented as increased areas of minimal flow in NTG patients. The preponderance of minimal flow and other low flow areas, compared with the age matched controls, indicates reduced flow within pixels at the 25th, 50th, and 75th percentile flow in NTG patients. These capillary perfusion differences were not detectable using “default” analysis of 10 × 10 pixel boxes, as placed within either the nasal or temporal peripapillary retina, or as averaged from these two areas.

The cSLDF was developed to measure capillary perfusion of tissue close to the site of nerve damage in glaucoma patients. Our findings directly document blood flow reductions within the peripapillary retina in NTG. These results are consistent with more indirect estimates of ocular perfusion (from indocya nine green angiography, colour Doppler imaging, and whole brain magnetic resonance imaging) suggesting that vascular dysfunction characterises this illness. Recent studies also suggest that primary open angle glaucoma (POAG) patients may suffer from blood flow reductions at the optic nerve head and in the peripapillary retina, further suggesting that blood flow deficits may be a consistent finding in glaucoma, independent of IOP.

The cSLDF accurately measures blood flow in an artificial capillary tube (r = 0.97, p < 0.0007), providing results similar to commercially available laser Doppler flowmeters. The method also displays coefficients of reliability near 0.85 for immediately repeated volume, velocity, and flow measurements from 10 × 10 pixel sampling sites. However, long term reproducibility from these small sampling boxes is less adequate, with the coefficient of variation of measures repeated each week for 4 weeks averaging 30% of the mean. A smaller sampling area (for example, a 4 × 4 pixel box) exacerbates these problems, and is even less reproducible than the larger box. However, broadening the analysis to include every qualifying pixel within the entire image (in this study, every qualifying pixel within the peripapillary retina) improves test/retest reliability, reducing the coefficient of variation of repeated weekly measurements to ~15% of the mean for selected portions of the flow histogram.

In summary, in this study cSLDF entire image analysis detected substantial reductions in capillary perfusion of the peripapillary retina in NTG patients compared with controls. The increase in minimal and low flow regions in these tissues in NTG show that reduced perfusion is certainly a correlate, and possibly a contributing cause, of the retinal ganglion cell death that defines this disease.
Dr Harris is the 1995 William and Mary Greve International Research Scholar.


