Correlation of retinal vascular caliber with severity of normal tension glaucoma

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Abstract

Purpose: Relationship of retinal vascular caliber with the severity of glaucomatous optic neuropathy (GON) in normal tension glaucoma (NTG) patients has not been reported in literature. We measured the retinal vascular caliber of NTG patients to correlate the caliber with the severity of GON.

Materials and methods: Cross sectional study in a tertiary care teaching Institute included sixty eyes of consecutive sixty NTG patients and sixty eyes (control) of consecutive sixty healthy individuals. Vascular caliber was measured at 0.5 disc diameter (DD) & 1DD away from disc margin on the segmented fundus image using MATLAB R2008A software. Artery to vein caliber ratio (AV ratio) was calculated. Main outcome measures were the correlation of vascular caliber with pattern standard deviation (PSD), mean deviation (MD) and vertical cup disc ratio (VCDR).

Results: Both mean arteriolar venular caliber at 0.5DD and 1DD was significantly narrow in NTG eyes compared to control. Correlation of pattern standard deviation (PSD) was observed with average arteriolar caliber at 1DD (r = -0.0361, p = 0.005); with AV ratio at both 0.5DD (r = -0.255, p = 0.049) and 1DD (r = -0.451, p = 0.000). No correlation of MD was observed with AV ratio, arteriolar caliber or venular caliber. Mean VCDR in NTG eyes (0.68 ± 0.11) was correlated with mean AV ratio at 0.5 DD (0.60 ± 0.08; r = -0.434; p = 0.001) and at 1DD (0.61 ± 0.11, r = -0.534; p = 0.000).

Conclusions: Our study indicates correlation of thinning of retinal vessels, arterioles in particular, with glaucomatous field loss and increased cup disc ratio in NTG patients.

Keywords: normal tension glaucoma, retinal vascular caliber, open angle glaucoma, glaucomatous optic neuropathy, retinal vessel.

Normal tension glaucoma (NTG) is defined as an optic neuropathy characterized by optic disc excavation and visual field loss with open angle and statistically normal intraocular pressure (IOP)¹. Although IOP is the most important risk factor for the development of glaucomatous optic neuropathy (GON) other risk factors also exist. Instability of ocular blood flow leading to a repeated mild reperfusion injury has been proposed in the pathogenesis of GON². Ischemia may play a central role in major stimuli for retinal ganglion cell apoptosis and inadequate perfusion of neural tissues resulting from vasoconstriction may cause characteristic visual field loss.³ NTG can be considered a part of the spectrum of primary open-angle glaucoma (POAG). While elevated IOP is the predominant cause in the pathogenesis of the GON in POAG, IOP-independent factors influence the pathogenesis of GON in NTG¹.

Among NTG patients, in whom elevated IOP is by definition absent, risk factors other than IOP may play an important role. NTG has been reported to be associated with hemodynamic crisis⁴, reduced ocular pulse amplitudes⁵, focal arterial narrowing around the optic nerve head⁶ and increased vascular resistance of ophthalmic artery⁷. NTG has also been reported to be associated with myocardial ischemia⁸, migraine⁹ and reduced blood flow to fingers¹⁰. NTG patients with lower heart-rate variability (suggesting autonomic dysfunction) demonstrated faster rate of central visual field loss progression compared to patients with higher heart-rate variability¹¹. All these provide indirect evidence for the role of vascular insufficiency in the pathogenesis of NTG.

Studies have shown that generalized retinal arteriolar narrowing is significantly associated with optic nerve damage in open angle glaucoma¹². One study concluded...
that narrowing of retinal arterial and venular caliber with glaucomatous optic neuropathy was independent of intraocular pressure (IOP)\textsuperscript{13}. Narrower mean retinal arteriolar and venular calibers in primary open angle glaucoma (POAG) compared to normal has been reported\textsuperscript{14}. Narrower retinal vessel calibers has been reported to be associated with reduced retinal nerve fiber layer (RNFL) thickness in an Asian population with POAG\textsuperscript{15}.

Relation of generalized narrowing of the retinal arteries to the severity of GON has been reported in POAG\textsuperscript{16}. Decrease in parapapillary retinal vessel diameters has been observed with advanced GON\textsuperscript{17}. Retinal arteriolar narrowing has also been reported to be associated with long-term risk of POAG\textsuperscript{18}. One recent study with NTG patients found significantly smaller mean diameter of the temporal retinal vessels in the quadrants with RNFL defects compared to quadrants without RNFL defects\textsuperscript{19}.

Relationship of retinal vascular caliber with the severity of GON in NTG has not been reported in literature (Medline and Scopus search). In this study we measured the retinal vascular caliber of NTG patients to correlate the caliber with the severity of disease.

**Materials and Methods:**

Normal tension glaucoma was defined in this study as eyes with glaucomatous optic nerve head and visual field (VF) damage with normal appearing anterior chamber angle and IOP<21 mm Hg (with 2 hourly IOP measurement over a 24 hour period). Glaucomatous VF (SITA Standard 30-2 test, Carl Zeiss Meditec, Dublin, CA, USA) was defined according to abnormality criteria proposed by Anderson\textsuperscript{20}. Sixty eyes of consecutive 60 NTG patients were included over a period of 2 years. Persons with past history of steroid use by any route, ocular trauma/surgery, optic neuritis, hemodynamic crisis were excluded. Eyes with congenital optic nerve abnormality, IOP>21 mm Hg on any occasion (from past document) were excluded. The eye with higher mean deviation (MD) was included as study eye in bilateral NTG. Sixty eyes of consecutive 60 normal healthy individuals were included as control by simple 1:1 randomization by tossing a coin. Vertical cup disc ratio (VCDR) was assessed in each case by a single masked observer (MB) with 11 years experience in glaucoma practice.

Color and red free images were taken in 35U field with the optic disc in centre (TRC 50 DX Topcon, Japan) by a single photographer (SM). Total observational magnification was 13x. After pre processing of the image, segmentation was done using Mahalanobis distance (a statistical distance function). The method has been reported previously in detail (available online at http://ophthalmicresearch.in/journals.html).\textsuperscript{21} In short, the preprocessed (histogram equalized) input image was considered to be the feature set for discrimination of four target classes in the image: class 1 = optic disc (OD), class 2 = artery, class 3 = vein, class 4 = background. Optic disc was segmented out and its diameter (DD) was measured in terms of number of pixels. Two circles were drawn at radial distances half disc diameter (0.5DD) and one disc diameter (1DD) distance apart from the margin of optic disc as described in literature.\textsuperscript{22} Segmentation of the background (i.e. class 4) was done and merged with OD segmented images (Fig. 1a and 1b).
Edge detection was performed. Instead of measuring average caliber of a vascular segment between 0.5DD and 1DD on the processed image in all cases by a single masked observer (SC). Two points were marked on the walls of a vessel where they were intersected by concentric circles. The distance was measured in unit of pixel. Pixel value was transformed into true diameter (in millimeter), by multiplying with converting factor. Vessel calibers were measured using MATLAB R2008A software. Artery to vein caliber ratio (AV ratio) was calculated. Comparison of vascular calibers was done using student t test. Correlation of vascular caliber with PSD, MD and VCDR was determined using Pearson’s correlation test. Data analysis was done by statistical software IBM SPSS version 19. Institutional ethics committee permitted the study.

Result:

Out of sixty NTG patients 32(53.3%) were male and 28(46.7%) were female. Among the control 30(50%) were male, rest were female. No significant difference in sex distribution was noted between two groups by Pearson Chi-Square test (p=0.715). Mean age was 60.7± 5.6 and 58.2± 5.8 years in NTG patients & control respectively. No significant difference was observed in age distribution between two groups by Levene’s test for equality of variances (p=0.917).

Mean VCDR were 0.68±0.11and 0.36 ±0.14 in NTG and control eyes respectively. In NTG eyes neuroretinal rim loss was most common infero-temporally, seen in 28(46.7%) eyes. Peripapillary hemorrhage was also most frequently seen infero-temporally, in 11(18.3%) NTG eyes.

In NTG eyes mean arteriolar diameter at 0.5DD (0.091±0.026mm) was significantly narrow globally (average of caliber in all quadrants) compared to control (0.119±0.022mm). Mean arteriolar diameter at 1DD (0.086 ±0.020mm) was also significantly narrow globally compared to control (0.117 ±0.021mm). When quadrant-wise analysis was done, mean arteriolar diameter was significantly narrow in all quadrants at 0.5 DD and in all except inferonasal quadrant at 1DD (table1).

We observed significant narrowing of average venular caliber in NTG eyes (0.151±0.025mm) compared to control (0.178±0.026mm) globally at 0.5 DD. Average venular caliber was significantly narrow also at 1DD (0.139±0.021mm) globally compared to control (158±0.020mm). When quadrant wise analysis was done, mean arteriolar diameter was significantly narrow in all quadrants at 0.5 DD and in all except inferonasal quadrant at 1DD (table 1).

Correlation of pattern standard deviation (PSD) was observed with average arteriolar caliber at 1DD(r= -0.0361, p=0.005). Correlation of PSD with AV ratio at both 0.5DD (r= -0.255, p=0.049) and 1DD(r= -0.451, p=0.000) was also observed. No correlation of PSD was observed with

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Table-1: Comparison of vessel caliber (in millimeter) at different quadrants between normal tension glaucoma and control eyes

<table>
<thead>
<tr>
<th></th>
<th>Global</th>
<th>ST</th>
<th>IT</th>
<th>SN</th>
<th>IN</th>
</tr>
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<tbody>
<tr>
<td>Art at 0.5 DD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTG</td>
<td>0.091±0.026</td>
<td>0.094±0.022</td>
<td>0.093± 0.035</td>
<td>0.083±0.023</td>
<td>0.093 ±0.027</td>
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<tr>
<td>Control</td>
<td>0.119±0.022</td>
<td>0.134±0.021</td>
<td>0.109±0.023</td>
<td>0.004“</td>
<td>0.109±0.011</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001*</td>
<td>&lt;0.001”</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Art at 1 DD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTG</td>
<td>0.086±0.020</td>
<td>0.083±0.019</td>
<td>0.092±0.029</td>
<td>0.073 ± 0.023</td>
<td>0.097±0.010</td>
</tr>
<tr>
<td>Control</td>
<td>0.117 ±0.021</td>
<td>0.127±0.021</td>
<td>0.114±0.022</td>
<td>0.117±0.019</td>
<td>0.112±0.020</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001*</td>
<td>&lt;0.001”</td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>0.269</td>
</tr>
<tr>
<td>Ven at 0.5 DD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTG</td>
<td>0.151±0.025</td>
<td>0.136±0.035</td>
<td>0.139± 0.045</td>
<td>0.141±0.036</td>
<td>0.146 ±0.027</td>
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<tr>
<td>Control</td>
<td>0.178±0.026</td>
<td>0.180±0.032</td>
<td>0.156±0.036</td>
<td>0.145±0.024</td>
<td>0.157 ±0.038</td>
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<tr>
<td>p</td>
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<td>0.006”</td>
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<td>0.408</td>
<td>0.610</td>
</tr>
<tr>
<td>Ven at 1 DD</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>NTG</td>
<td>0.139±0.021</td>
<td>0.149±0.011</td>
<td>0.149±0.034</td>
<td>0.124±0.020</td>
<td>0.143±0.039</td>
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<tr>
<td>Control</td>
<td>0.158±0.020</td>
<td>0.184±0.012</td>
<td>0.154±0.037</td>
<td>0.147±0.017</td>
<td>0.145 ±0.026</td>
</tr>
<tr>
<td>p</td>
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<td>&lt;0.001”</td>
<td>0.604</td>
<td>0.001”</td>
<td>0.745</td>
</tr>
</tbody>
</table>

*Significant at the 0.05 level, **significant at the 0.01 level, ST= superotemporal, IT= Inferotemporal, SN= Superonasal, IN= Infereonasal, Art= Average arteriolar caliber, Ven= Average venular caliber, DD= disc diameter NTG= normal tension glaucoma
venular caliber and arteriolar caliber at 0.5 DD. No correlation of MD was observed with AV ratio, arteriolar caliber or venular caliber (table 2).

Mean VCDR in NTG eyes (0.68±0.11) was correlated with mean AV ratio at 0.5 DD (0.60±0.08; r= -0.434; p=0.001) and at 1DD (0.61±0.11, r= -0.534; p=0.000).

Discussion:

In this study retinal vessel caliber was measured from fundus photographs by a newer technique. In the existing method Gaussian curve fitting is done over the actual intensity line profile of the vessel. This may give some erroneous vessel width. The method used in the present work relies on segmentation by manual marking of the pixels over different study classes to calculate their respective covariance matrices used in Mahalanobis distance function taking care of the correlation of different variables in the feature set. In our study the average arteriolar and venular caliber was lower than that reported in previous studies. However our study result is nearer to the widely accepted width of a venule as the width of a major vein at the disc edge is considered to be 125µ. The measurements of average venular caliber in normal eyes in previous studies are clearly much more (222.9µ, 219.7 µ) than the width(125µ) universally accepted for clinical use.

In current study, both average arteriolar caliber and average venular caliber were found narrower in NTG compared to control. Previous studies with vessel caliber in POAG revealed variable observations. In an Asian population with POAG narrower arteriolar and venular calibers was noted compared to normal. The Blue Mountains Eye Study reported significant narrowing only in arteriolar diameters. Focal arteriolar narrowing was reported in POAG and NTG compared to control. The Beaver Dam Eye Study and the Rotterdam Study did not find association of retinal vascular caliber with POAG.

We observed significant correlation of PSD with average arteriolar caliber at 1DD as well as with AV ratio at both 0.5DD and 1DD. However no such correlation was observed with MD. MD is mainly an index of the size of visual field defect while PSD is an index of localized non uniformity in the field. NTG patients are known to have deeper and more localized scotomas. This may explain the relationship of PSD and MD with AVR in our study.

In our study, neuroretinal rim loss and peripapillary haemorrhage was most frequent inferotemporally. However superonasal quadrant was the only quadrant demonstrating both arteriolar and venular narrowing at 0.5DD as well as 1DD in our study. Neuroretinal rim loss and peripapillary haemorrhage were thus could not be related to vascular narrowing in general. Interestingly inferotemporal quadrant was the only quadrant demonstrating significant arteriolar narrowing at both distances with absence of any venular narrowing. This implies that arteriolar narrowing in the absence of venular narrowing was associated with increased incidence of neuroretinal rim loss and peripapillary haemorrhage in our study.

Our study indicates correlation of thinning of retinal vessels, arterioles in particular, with glaucomatous field loss and increased cup disc ratio in NTG patients. Our results support the associations previously reported between vascular caliber and NTG.

Quantitative measurement of vascular caliber may thus play adjunctive diagnostic role in the assessment of NTG patients. Prospective studies will provide a clearer answer to the key question of whether quantitative measurement of retinal vascular calibre may be used to predict the development and/or progression of NTG.

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Reference:


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