Significance of non-intraocular pressure (IOP)-related factors particularly in normal tension glaucoma: Looking beyond IOP

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Purpose: To study the relationship between intraocular pressure (IOP) and mean ocular perfusion pressure (MOPP) in patients with POAG and NTG. The secondary objective was to identify other contributory ischemic factors. Methods: This was an observational cross-sectional study from a tertiary eye hospital in patients who underwent full-day diurnal variation of tension (DVT). Blood pressure (BP) and IOP measurements were done every 3 h over 24 h. Mean arterial pressure (MAP) and MOPP were calculated. The nocturnal dip in BP was assessed; patients were classified as non-dippers, dippers, and over-dippers. The circadian MOPP fluctuation (CMF) was calculated using the Kruskal–Wallis test, and its relationship with type and severity of visual field was assessed. Results: In total, 149 patients were evaluated; 109 were classified as NTG, and 40 were classified as POAG. A nocturnal dip in BP was noted in 20% of NTG and 17.5% of POAG. The MAP was found to be lower in patients with NTG than POAG. In the NTG subgroup, we found that 20% of patients were over-dippers, 32% were dippers, and 48% were non-dippers. The CMF showed a greater fluctuation for over-dippers (P = 0.004 for the RE and 0.003 for the LE) than dippers and non-dippers. A weak positive correlation of CMF with the severity of fields was found. Conclusion: A 24-h monitoring of IOP, BP, MOPP, and assessment of systemic risk factors for primary glaucoma acts as an invaluable tool for the comprehensive management of NTG despite the limitations posed by DVT and BP recording.

Key words: Carotid artery disease in NTG, diurnal variation of IOP, ischemia in glaucoma, mean ocular perfusion pressure, normal-tension glaucoma

Intraocular pressure varies during a 24-hour period, which is known as a diurnal variation in tension (DVT).\(^{[1,2]}\) Raised IOP and IOP fluctuations are closely associated with glaucoma progression.\(^{[3,4]}\) However, there is insufficient evidence to state that short-term IOP variations are an independent risk factor.\(^{[5,6]}\) Various studies have pointed out the importance of vascular factors in the development of NTG, including migraine, Raynaud’s phenomenon, blood transfusion, atherosclerotic factors, vasospastic disorders, and nocturnal dip of blood pressure.\(^{[7,8]}\) Obstructive sleep apnea syndrome (OSAS), an under-reported systemic disorder, is also known to have an IOP independent association with glaucoma and its progression.\(^{[9,10]}\) Collaborative Normal-Tension Glaucoma Study (CNTGS) reported that 20% of normal-tension glaucoma (NTG) patients progress despite a 30% reduction in IOP, indicating the importance of non-IOP-related factors in optic nerve head (ONH) damage.\(^{[11]}\) Thus, in NTG, detecting and treating the cause of ONH ischemia in addition to IOP control may prevent or slow down the progression of the disease. Previous studies have reported that systolic ocular perfusion pressure, mean ocular perfusion pressure (MOPP), and mean arterial pressure (MAP) are important in glaucoma progression.\(^{[11-13]}\) Tokunaga et al.\(^{[11]}\) reported that in NTG or primary open-angle glaucoma (POAG), non-physiologic nocturnal blood pressure (BP) reduction was related to glaucoma progression at 4-year follow-up and emphasized that hemodynamic parameters are possible risk factors for glaucoma progression. Various studies have also pointed out that poor ocular perfusion pressure could lead to chronic ONH insufficiency and thereby progression of visual field defects.\(^{[14]}\)

We hypothesize that a significant number of NTG patients have nocturnal dips in BP and compromised ocular blood perfusion along with associated systemic issues. Furthermore, a significant number of POAG patients may be missed if diagnosis is made based on office-hour IOP alone. Thus, we studied the BP fluctuation throughout the day, in addition to DVT, and also attempted to look beyond IOP, at other systemic risk factors responsible for causing glaucoma, hoping to widen our knowledge and armamentarium of treatment.

Methods

A retrospective, cross-sectional review of the medical records of patients admitted for 24-h DVT and diurnal variation of blood pressure (DVPB) from January 2012 to February 2020 in a tertiary eye care center was performed. Patients presenting to the glaucoma clinic with disc and visual field changes with open angles on gonioscopy but normal office IOP and no secondary
factors for glaucoma were subjected to full-day DVT and DVBP as routine clinical practice. Patients with inflammatory glaucoma, pseudoexfoliation glaucoma, neovascular-glaucoma, steroid-induced glaucoma, secondary glaucomas, and those already on anti-glaucoma medications (AGM) were excluded. We excluded patients with intracranial neoplasms, previous history of stroke, and conditions causing neurological field defects. All patients underwent refraction, Goldmann applanation tonometry (GAT), slit-lamp evaluation, gonioscopy, pachymetry, and stereoscopic disc evaluation. Disc changes such as a cup:disc ratio of more than 0.7, asymmetry of more than 0.2 between the two eyes, diffuse or localized neuroretinal rim thinning, disc hemorrhages, or retinal nerve fiber layer (RNFL) defects were considered to be glaucoma suspects. These patients were subjected to perimetry with the Humphrey field analyzer (Carl Zeiss Meditec, Model 745i) or an ONH imaging technique, that is, Heidelberg retinal tomogram (HRT3) or optical coherence tomography (OCT). Diagnosis of glaucoma was made based on a reliable perimetry report following Anderson’s criteria and/or imaging reports along with clinical correlation with disc findings. If office IOP recorded on GAT was <21 mm Hg, they were advised a full-day DVT and DVBP. These patients were admitted and underwent an IOP check with GAT and BP measurement (Omron Model HEM 7201) every 3 h for 24 h. IOP was measured with the same GAT and by the same doctor to minimize inter-observer errors. The IOP readings were corrected for central corneal thickness (CCT) and used for the calculations.

Patients who had an IOP recording of >21 mm Hg any time during the 24-h period were labeled as POAG, and those who had all recordings of <21 mm Hg were labeled as NTG.

The mean arterial pressure (MAP) was calculated using the following formula:

\[ \text{MAP} = \text{DBP} + \left[ \frac{1}{3} \times \left( \text{SBP} − \text{DBP} \right) \right] \]

Mean ocular perfusion pressure (MOPP) was estimated using the following formula:

\[ \text{MOPP} = \frac{2}{3} \times \frac{\text{MAP} − \text{IOP}}{} \]

The patients were classified as dippers and non-dippers based upon their nocturnal blood pressure dip by using the following formula:

\[ \left[ \frac{\text{diurnal average BP} − \text{nocturnal lowest BP}}{\text{diurnal average BP}} \right] \times 100 \]

Patients were classified based on the nocturnal BP reduction as non-dippers (<5% reduction), dippers (5%–10% reduction), and over-dippers (>10% reduction).

The subgroup of patients characterized as POAG was started on treatment with AGM. The NTG patients were also started on AGM and advised to undergo echocardiography, carotid Doppler, and a cardiology consultation.

The data were analyzed using 2-way analysis of variance to determine the difference in IOP, BP, MAP, and MOPP across the POAG and NTG groups at all time points using Medcalc version 12.5.0.0. The percentage of patients in whom ischemic factors (such as low diastolic BP) or significant changes on cardiac investigations and other systemic investigations could be identified was determined.

Furthermore, we analyzed the difference between POAG and NTG patients with respect to the severity of glaucoma based on mean deviation (MD) on visual fields. As NTG is known to have more central defects, the types of field defects were also studied in both groups. To categorize the defects as central or peripheral, the ratio of the mean of the data points in the central 10 degrees to that of the peripheral 14 degrees on the numeric plot of the 24-2 program on Humphrey’s visual field was taken. A ratio of >1 signified that the defects were more peripheral as the threshold sensitivities were higher in the center, and a ratio of <1 suggested more central defects.

### Results

Table 1: Demographic data and classification of patients as normal-tension glaucoma (NTG) and primary open-angle glaucoma (POAG) with office and non-office hour intraocular pressure (IOP) recordings

| Gender (Male:Female) | NTG (n=109) | POAG (n=40) |
|----------------------|------------|------------|
| Age (Years)          | 59.42±11.7 (Mean±SD) | 55.09±12.64 (Mean±SD) |
|                      | 53:56      | 25:15      |
| Office hours         |            |            |
| IOP Right Eye (mm Hg)| 15.23±0.25 | 20.38±0.30 |
|                      | <0.001     | 19.44±0.41 |
| IOP Left Eye (mm Hg) | 15.22±0.17 | 20.1±0.22  |
|                      | <0.001     | 19.11±0.25 |
| Systolic BP (mm Hg)  | 128.71±1.77| 129.85±1.23|
|                      | 0.210      | 129.11±1.98|
| Diastolic BP (mm Hg) | 78.25±0.77 | 80.23±0.9  |
|                      | 0.013      | 80.67±0.81 |

In the NTG group, 22 (20%) patients based on a nocturnal dip were classified as over-dippers, 35 (32%) as dippers, and 52 (48%) as non-dippers. In the POAG group, 7 (17.5%) patients were classified as over-dippers, 18 (45%) as dippers, and 15 (37.5%) as non-dippers.

In the NTG group, we found that over-dippers had a higher diurnal MOPP as compared to nocturnal MOPP (53.176 ± 4.3,
52.685 ± 5.3 in the RE; 53.17±4.3, 52.87 ± 5.3 in the LE). In the non-dipper group, we found the nocturnal MOPP to be higher than diurnal MOPP (55.46 ± 6.5, 56.74±7.2 in the RE; 55.63 ± 6.5, 56.85 ± 7.19). However, this difference was not statistically significant ($P = 0.739$) for the over-dipper group and for the non-dipper group ($P = 0.343$) (RE) and in the over-dipper group ($P = 0.841$) and in the non-dipper group ($P = 0.370$) (LE).

In the POAG group, we found that the over-dippers had a higher nocturnal MOPP than diurnal MOPP (54.25 ± 7.66, 53.75 ± 7.79 in the RE; 53.70 ± 7.17, 53.57 ± 6.63 in the LE). In the non-dipper subset of patients also, the nocturnal MOPP was higher than the diurnal MOPP (50.84 ± 7.55, 49.92 ± 6.55 in the RE; 50.84 ± 7.62, 49.79 ± 6.55 in the LE). Again, this difference did not show a statistical significance, with $P = 0.906$ for the over-dipper group and 0.725 for the non-dipper group (RE) and 0.973 for the over-dipper group and 0.688 for the non-dipper group (LE).

The circadian MOPP fluctuation (CMF) was calculated as the difference between the highest and lowest MOPP values recorded during the 24-h phasing. The CMF calculated using the Kruskal–Wallis test showed a greater fluctuation for over-dippers than dippers and non-dippers ($P = 0.004$: RE; 0.003: LE) [Fig. 3].

The average mean deviation (MD) on perimetry was –8.58 for RE and –8.56 for LE for the NTG group, and –10.86 for RE and –10.63 for LE for the POAG group. The type of field defects was similar in both groups as the mean ratio of central to peripheral threshold sensitivities was 1.22 and 1.23 for RE and LE, respectively, for the NTG group, and 1.196 and 1.15 for RE and LE, respectively, for the POAG group. We analyzed the correlation between CMF and MD of visual fields; it showed a weakly positive correlation using Pearson’s correlation coefficient (0.04) for BE.

The NTG subgroup underwent a cardiology opinion, carotid Doppler, and an echocardiogram, of whom 9 patients were found to have cardiac abnormalities and 1 was diagnosed with OSAS [Table 2]. Of these 9 patients, 3 were diagnosed with coronary artery disease (CAD) and 2 underwent an immediate coronary artery bypass grafting (CABG); 1 was found to have 75% carotid artery stenosis and underwent carotid endarterectomy. One patient who was found to have normal cardiac evaluation initially was further evaluated in view of glaucoma progression and was diagnosed with OSAS and was started on continuous positive airway pressure (CPAP). The remaining 6 patients had mild cardiac abnormalities and were advised observation and follow-up. The clinical characteristics of these patients, that is, IOP pattern, BP fluctuations, and pattern of field loss and glaucoma severity, were not different from the rest of the NTG patients.

To summarize, in our study, 73.15% of patients included were classified as NTG and 26.84% as POAG after a 24-h DVT. In the POAG group, 35% of patients showed a peak IOP in the non-office hours. A similar proportion of patients were found to have a nocturnal dip in BP in both groups, that is, 18% of NTG and 22% of the POAG group. In the NTG group, 20% of patients were classified as over-dippers and these had a higher diurnal MOPP as compared to nocturnal MOPP. In the NTG subgroup, 8.25% of patients were found to have cardiac abnormalities and 1% were diagnosed with OSAS; of these, 2 had to undergo immediate surgical intervention.
Discussion

Glaucoma is a multifactorial disease characterized by loss of retinal ganglion cells (RGCs) that leads to a distinctive optic neuropathy and visual field loss. IOP control has so far been the only proven method of controlling glaucoma progression. There is a strong need to address pressure independent factors, particularly in NTG patients or patients with glaucoma progression despite IOP control. A 24-h DVT though ideal is not very popular, being limited by inadequate infrastructure in many eye hospitals. In our study, we found 73.15% of suspected patients with normal-office IOP were diagnosed to have NTG after the 24-h DVT, that is, 1/3rd (26.84%) of the patients belonged to POAG, and IOP spikes were missed during office hours. In addition, peak IOP for both the groups was noted during non-office hours, indicating those could be missed without DVT. A study done in Japan by Shiose et al. estimated the prevalence of NTG to be 1/3rd of the total POAG cases. The Beaver Dam study estimated the prevalence of NTG to be around 1/3rd of the POAG cases. They also found that the possibility of NTG increased from 0.2% in those aged 43–54 to 1.6% in the above-75 age group. We found that 5.5% of our NTG cohort was below 40 years of age. Thus, it is important to identify patients of POAG with IOP spikes in non-office hours who may not require additional investigations like NTG patients. Furthermore, the high incidence of NTG in the younger population necessitates early detection to prevent the loss of sight years.

In addition to recording IOP during a 24-h DVT, the recording of BP is important. Among NTG patients, 20% were found to have a nocturnal dip in blood pressure. Yazici et al. reported a repeated, excessive dip in nocturnal BP levels in NTG patients as compared to POAG and OHT patients; however, in our study, a similar nocturnal dip was seen in both groups. We also found that 22% of NTG patients were over-dippers, reaffirming the vascular etiology theory. Choi et al. reported 41% of over-dippers in their subset of NTG patients. Graham et al. reported lower pressure parameters in 37 patients with progressive field defects compared to 15 patients with stable field defects, concluding that nocturnal BP reduction could be an additional risk factor for glaucoma progression. In our study, over-dippers had a higher diurnal MOPP than nocturnal MOPP, and non-dippers had a higher nocturnal MOPP than diurnal MOPP; the inverse was true in POAG. This difference was not statistically significant; however, it does indicate a difference in the pattern of ocular perfusion in dippers, non-dippers, and over-dippers. Tokunaga et al. found that a nocturnal dip deviating from the physiological range was associated with glaucoma progression, though there was no correlation between the magnitude of the dip or in the rate of progression between NTG and POAG patients. Deb et al.

Table 2: List of systemic findings in normal-tension glaucoma (NTG) patients

| Gender | Age (Years) | Systemic Findings |
|--------|-------------|-------------------|
| Female | 71          | Left ventricular hypertrophy with sclerosed aortic valve |
| Male   | 60          | Underwent coronary artery bypass graft surgery |
| Male   | 54          | Right common carotid artery plaque with 35% stenosis |
| Male   | 57          | Underwent endarterectomy |
| Male   | 66          | Left common carotid artery showed 15% stenosis, left ventricular ejection fraction 55%, mild tricuspid regurgitation |
| Male   | 77          | Right common carotid artery stenosis |
| Female | 64          | Diagnosed with coronary artery disease |
| Male   | 64          | Underwent coronary artery bypass graft surgery |
| Female | 74          | Left ventricular hypertrophy with regurgitation |
| Male   | 51          | Obstructive sleep apnea |

Figure 3: Circadian mean ocular perfusion pressure fluctuation (CMF) for dippers, non-dippers, and over-dippers for the right and left eyes
evaluated perfusion pressure in patients with POAG versus normal and reported that increased MOPP had a reduced risk of glaucoma. They also pointed out an increased risk for POAG in hypertensive patients and attributed to anti-hypertensive treatment, causing nocturnal dips in BP compromising ocular blood flow highlighting a vascular association.\[21\] This is evident in our study as well because we found a nocturnal dip in BP in 17.5% of POAG patients. We also noted a statistically significant difference in the CMF, with over-dippers showing a higher fluctuation than both the dippers and non-dippers, indicating greater variability in ocular perfusion leading to multiple ischemic insults resulting in glaucomatous ONH damage. This reiterates our recommendation for identifying patients that need treatment for the nocturnal dip in BP, in addition to glaucoma management, to prevent progression.

In our study, 9% of NTG patients were diagnosed to have systemic issues, including cardiac disease and OSAS, that required immediate intervention. This implies that the timely identification and management of systemic issues would not only help to prevent glaucoma progression but may also help reduce overall morbidity and mortality in these patients. In fact, glaucoma may be a warning sign to something bigger and timely intervention might prevent a debilitating condition.

Some studies have correlated the vascular perfusion factors with severity of visual fields. Hayreh et al.\[22\] assessed visual field deterioration in 64 patients with glaucoma but did not find a significant difference with BP parameters compared to patients with stable visual fields. In our study, we correlated CMF with MD of glaucomatous VF defects and found a weakly positive correlation; however, our cohort had different stages of the disease, and the association may vary based on the severity. A longitudinal study may help correlate it to progression as well and help us understand how patients who progress despite well-controlled IOP can be managed better.

Our study is limited by small numbers although it is comparable to other similar studies. Moreover, we did not assess the systemic factors in POAG patients (the cohort that did not undergo DVT) due to the retrospective nature of our study. Furthermore, we have to keep in mind that ocular perfusion values determined using formulae may vary compared to an actual measurement. Thus, the advent of noninvasive methods and continuous IOP monitoring systems might throw more light on IOP and CMF patterns affecting glaucomatous ONH changes.

**Conclusion**

In conclusion, 24-h monitoring of IOP helps differentiate between POAG and true NTG patients and helps in better management of this subset of patients. Monitoring BP and MOPP as well as assessing associated systemic risk factors can prove invaluable for comprehensive management of NTG and early treatment of associated systemic disorders.

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**Conflicts of interest**

There are no conflicts of interest.

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