Glaucomatous Optic Neuropathy Associated with Nocturnal Dip in Blood Pressure

Findings from the Maracaibo Aging Study

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Purpose: To determine which nocturnal blood pressure (BP) parameters (low levels or extreme dipper status) are associated with an increased risk of glaucomatous damage in Hispanics.

Design: Observational cross-sectional study.

Participants: A subset (n = 93) of the participants from the Maracaibo Aging Study (MAS) who met the study eligibility criteria were included. These participants, who were at least 40 years of age, had measurements for optical tomography coherence, visual field (VF) tests, 24-hour BP, office BP, and intraocular pressure < 22 mmHg.

Methods: Univariate and multivariate logistic regression analyses under the generalized estimating equations (GEE) framework were used to examine the relationships between glaucomatous damage and BP parameters, with particular attention to decreases in nocturnal BP.

Main Outcome Measures: Glaucomatous optic neuropathy (GON) based on the presence of optic nerve damage and VF defects.

Results: The mean age was 61.9 years, and 87.1% were women. Of 185 eyes evaluated, 50 (27.0%) had signs of GON. Individuals with GON had significantly lower 24-hour and nighttime diastolic BP levels than those without. However, results of the multivariate GEE models indicated that the glaucomatous damage was not related to the average systolic or diastolic BP levels measured over 24 hours, daytime, or nighttime. In contrast, extreme decreases in nighttime systolic and diastolic BP (>20% compared with daytime BP) were significant risk factors for glaucomatous damage (odds ratio, 19.78 and 5.55, respectively).

Conclusions: In this population, the link between nocturnal BP and GON is determined by extreme dipping effects rather than low nocturnal BP levels alone. Further studies considering extreme decreases in nocturnal BP in individuals at high risk of glaucoma are warranted. Ophthalmology 2017; - 1–8 © 2017 by the American Academy of Ophthalmology

Supplemental material available at www.aaojournal.org.
average nighttime BP levels, contributes to glaucomatous optic neuropathy (GON).

Methods

Sample Population

We studied 93 MAS participants who were evaluated for eye health and who met the selection criteria described next.15 The MAS—a population-based epidemiologic study of age-related traits—currently includes approximately 3000 individuals, ≥40 years of age, living in the Santa Lucia neighborhood15 or in the nearby community of Santa Rosa de Agua15 in Maracaibo, Venezuela; all MAS participants received standardized assessments.15 Randomly selected participants were invited to undergo an ophthalmological assessment. To be included in this study, individuals had to have completed OCT scans, visual field (VF) tests, ABPM, and office BP measurements. We decided to exclude 1 individual with an IOP ≥22 mmHg, which we believed would only add uncertainty to results. Ninety-three individuals met the criteria. Each participant signed an informed consent, which was approved by the Institutional Review Boards of the Cardiovascular Institute at University of Zulia and Columbia University.

Ophthalmological Assessment

Ophthalmologists conducted an ocular assessment of both eyes. This assessment included clinical ocular history; best-corrected visual acuity; a slit-lamp examination (gonioscopy); and a dilated evaluation of the lens, vitreous, and retina. The IOP was estimated with Goldmann tonometry. Standard automated perimetry was performed with the Heidelberg Edge Perimeter (Heidelberg Engineering, GmBH, Heidelberg, Germany). Spectralis spectral-domain (SD) OCT (software version 5.4.7.0; Heidelberg Engineering, GmBH) was used to measure the thickness of the peripapillary retinal nerve fiber layer (RNFL). Peripapillary RNFL measurements were obtained in a circle scan centered on the optic disc. The RNFL analysis used an automated computer algorithm to identify the anterior and posterior margins of the RNFL, from which the RNFL thickness was calculated. In addition, if the visual acuity was 20/20 or better in each eye according to the Standard Early Treatment Diabetic Retinopathy Study protocol at 4 m, refraction was performed following standard protocols.

Glaucomatous optic neuropathy diagnosis based on clinical examination and confirmation with SD OCT abnormalities had to include at least 2 peripapillary sectors flagged as “borderline” (P < 0.05) or 1 sector “outside normal limits” (P < 0.01). All patients underwent clinical examination with indirect ophthalmoscopy with a 78/90 diopter lens. In addition, reflectance images of the optic disc were evaluated, looking for signs of cupping and RNFL thinning. Finally, the attending clinician and OCT/VF reader followed the recommendations of the American Academy of Ophthalmology Preferred Practice Patterns.12 The OCT RNFL b-scans had to be free of segmentation errors and blinking/eye movement artifacts. The VF abnormalities required at least 3 neighboring points that were 5%, 5%, and 1% probability, or 5%, 2%, and 2% probability or poorer within a hemifield on pattern deviation plots, with only 1 point allowed on the edge of the VF. The VF results had false-negative, false-positive, and fixation-loss rates less than 30%. Glaucoma was diagnosed during the clinical optic disc evaluation and confirmed with SD OCT peripapillary RNFL thickness measurements, based on the presence of GON and VF abnormalities. Suspected glaucoma was diagnosed if the patient met the criteria for GON, but not for VF abnormality. The ophthalmologist determined, via gonioscopy, that all cases of GON identified in our population were open-angle. An abnormal optic disc was defined as diffuse or focal narrowing, or notchings, of the optic disc rim, or optic disc neural rim asymmetry of the 2 eyes consistent with loss of neural tissue. An abnormal VF, when present, was defined as (1) VF damage consistent with RNFL damage (e.g., nasal step, arcuate field defect, or paracentral depression in clusters of test sites) based on the presence of abnormal clusters; or (2) VF defects consistent with glaucomatous optic nerve damage.

The diagnosis of glaucoma or suspected glaucoma was performed by one of the investigators (CGDM) from the Optic Nerve and Visual Field Reading Center at Columbia University Medical Center in New York. Because of the small number of individuals with glaucoma in the study, we combined the 2 diagnostic groups (i.e., glaucoma and suspected glaucoma) as the main outcome measure of GON.

Blood Pressure Measurements

The office systolic BP and diastolic BP were obtained for each participant by trained nurses at the Cardiovascular Institute of the University of Zulia, using a validated automated device (Dynamap, XL). After participants had rested in a sitting position for 5 to 10 minutes, 5 consecutive (1 per minute) BP measurements were taken in a sitting position and averaged. The ABPM devices (validated oscillometric 90202 or 90207 SpaceLabs monitors, Redmond, WA) were programmed to obtain readings every 15 minutes during daytime hours (06:00-22:59) and every 30 minutes during nighttime hours (23:00-05:59). The hypertension diagnosis followed the guidelines of the European Societies of Cardiology and Hypertension, 2013. Office hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive drugs. The 24-hour BP, daytime BP, and nighttime BP measurements were the average BP recordings during the appropriate intervals. Ambulatory hypertension was defined as 24 hours of systolic BP ≥130, diastolic BP ≥80 mmHg, or the use of antihypertensive drugs.

Dipper statuses were defined as follows: (i) extreme dipper: an abnormal decrease in the nocturnal BP levels more than 20% in relation to diurnal BP levels; (ii) dipper: a normal decrease in the nocturnal BP levels between 20% and 10% in relation to diurnal BP levels; (iii) nondipper: a minor or no decrease in nocturnal BP levels, ranging from 10% to 0%; and (iv) reverse dipper: an abnormal increase in nocturnal BP levels in relation to daytime BP levels. To identify the decrease or increase in nocturnal BP levels in relation to daytime BP levels, we used the ABPM to calculate the night/day BP ratio, as suggested by Fagard et al.17 Night/day BP ratios ≤0.8 indicated an extreme dipper, >0.8 to 0.9 indicated a dipper, >0.9 to 1.0 indicated a nondipper, and >1.0 indicated a reverse dipper. Dipper status was determined separately for systolic BP and diastolic BP. We combined reverse dippers with nondippers for analysis because of the small number of participants who were reverse dippers and the fact that nondipper and reverse dipper status did not add any significant risk for GON (Table S1, available at www.aaojournal.org).

Other Information

Participants provided their medical history, including age, sex, level of education, smoking history, alcohol intake, and...
antihypertensive drug treatment. In addition, clinical and laboratory assessments were performed to measure total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and hemoglobin A1c. Body mass index (BMI) was calculated by kg/m². Diabetes mellitus was defined as a glucose serum level ≥126 mg/dl, hemoglobin A1c ≥6.5%, or intake of antidiabetic drugs.

Statistical Analyses

Categoric variables were compared for the 2 groups using the chi-square test, and continuous variables were compared using Student t test. To assess various BP parameters as risk factors for glaucomatous damage, we performed univariate and multivariate logistic regression analyses under the generalized estimating equations (GEE) framework to take into account nonindependence of the 2 eyes within an individual. Confounders were identified using a threshold of P < 0.1 in the comparison of baseline characteristics. However, despite the P value, the IOP was selected as a confounder because of its alluded role in the pathogenesis of GON. One multivariate model was adjusted only for age, and another model was fully adjusted for age, education level, BMI, LDL-cholesterol, creatinine, conventional hypertension, refractive error, and IOP. All the analyses were performed using SPSS 23 (IBM Corp., New York, NY). Statistical significance was accepted at P < 0.05 for 2-tailed tests.

Results

Sample Population

The mean age of the participants was 61.9 years, and 87.1% were women (Table 1). Some 28.0% were smokers, and 9.7% reported consuming alcohol. Approximately 14.0% had diabetes. The prevalence of hypertension based on office BP and ABPM was 64.5% and 55.9%, respectively, and 47.3% of those with office hypertension were taking antihypertensive medications. Table S2 (available at www.aaojournal.org) shows the comparison of the baseline characteristics between nonincluded and included individuals. Nonincluded individuals in the present study were older, were less frequently women, had fewer years of education, were more often smokers, had a higher proportion of alcohol intake, had a lower BMI, were more like to have hypertension, had lower levels of LDL cholesterol, had a history of cardiovascular diseases, had poorer treatment of hypertension, and had higher levels of conventional and ABPM.

Of the 93 participants, 26 (30.0%) had at least 1 eye with GON (Table 1). A total of 185 eyes were evaluated, and 49 eyes (26.6%) were identified as having GON: 19 (10.3%) as glaucoma and 30 (16.1%) as suspected glaucoma. One individual with an IOP ≥22 mmHg in 1 eye was excluded from the analysis. Individuals with GON were significantly older, had lower levels of education, had a lower BMI, and were more likely to have refractive errors than individuals with healthy eyes. The type of antihypertensive treatment was not associated with GON (Table S3, available at www.aaojournal.org).

Blood Pressure Levels and Glaucomatous Eyes

Office systolic BP levels were significantly higher in participants with GON than in individuals with healthy eyes (Table 2). In contrast, systolic BP levels based on 24-hour ABPM did not differ between GON and healthy eyes, but levels of diastolic BP, especially nighttime diastolic BP, were significantly lower in individuals with GON when compared with BP levels in those with healthy eyes. However, the 2 multivariate-adjusted GEE models showed levels of diastolic BP were no longer significantly associated with glaucomatous damage (Table 3).

Dipper Status and Glaucomatous Risk

We then further examined 24-hour BP by determining whether BP dipper status influenced GON. When the proportions of extreme dippers were compared between individuals with GON eyes and individuals with healthy eyes, 18.4% of the glaucomatous eyes had extreme dipper status by systolic BP, whereas just 3.0% of the healthy eyes did. Likewise, 34.7% of the glaucomatous eyes had extreme dipper status by diastolic BP, whereas 17.8% of the healthy eyes did (Fig 1). Under the fully adjusted multivariate GEE models, extreme dippers (systolic and diastolic) had a significantly higher risk of having glaucomatous eyes when compared with normal dippers (Table 4). Meanwhile, nondipper and reverse dipper effects were not associated with an increased risk of GON.

Discussion

This study suggests that the extreme decrease in BP as defined by a decrease >20% of nocturnal BP levels compared with daytime BP levels, rather than nocturnal hypotension per se, increases glaucoma risk. Individuals with low nighttime BP levels did not show elevated risk. Overall, our study demonstrated that after adjusting for confounders, systolic BP and diastolic BP levels, averaged for 24-hour, daytime, and nighttime intervals, were not significant risk factors for presence of GON, whereas extreme dipper systolic and diastolic status were associated with increased risk of GON.

The rates of glaucoma (10.3%), suspected glaucoma (16.1%), and GON (26.6%) were high in our study in contrast with Black-Hispanics living in Barbados or Mexican-Americans living in Los Angeles or Arizona, but were similar to rates of suspected glaucoma among Hispanics of Caribbean origin residing in New York. Populations from Maracaibo have a proportion of ancestral European, African, and Native American genetic contributions that have more in common with other Caribbean populations than with Mexican populations, which could explain the different proportion of individuals with glaucomatous damage. In addition, environmental exposures might explain the high rates of GON in the MAS population, including low socioeconomic status and the low Human Development Index that characterize this population. However, of particular importance for glaucoma risk is the high prevalence and low treatment and control rates of hypertension among the studied population.

The relationship between systemic BP levels and glaucoma pathogenesis has been extensively examined, and nocturnal hypotension is known to be a major risk factor for the prognosis and progression of glaucoma diseases. The proposed mechanism implicated is chronic ischemia. When BP levels decrease sharply during the night, systemic perfusion of the eye is inadequate. Autoregulation of eye circulation can normalize the
perfusion, but autoregulation might be compromised in individuals with glaucoma. In those individuals, the extreme reduction of perfusion pressure in the optic nerve head can lead to ischemia and, ultimately, to GON.19 Interestingly, low nighttime BP levels were not significantly associated with glaucomatous damage unless there was an extreme dipping effect.

Approximately 15% to 25% of individuals aged ≥40 years have an extreme dipper pattern, which has been linked to increased duration of heart ischemic episodes, cognitive decline, and silent brain infarction.23,24 Furthermore, extreme dipping status is associated with progression of glaucoma.20,25 Our study extends these findings in that (i) individuals with extreme dipping effect exhibited the highest increased risk for GON, and (ii) our results were determined in the general Hispanic population.

Our study showed that nocturnal BP measurements as measured by ABPM are more insightful indicators of

Table 1. Baseline Characteristics of the Total Population, Stratified by Individuals with Glaucamatus Optic Neuropathy and Healthy Eyes

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Total Population (n = 93)</th>
<th>Individuals with Glaucamatus Optic Neuropathy* (n = 26)</th>
<th>Individuals with Healthy Eyes (n = 67)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>61.9±13.3</td>
<td>70.9±12.1</td>
<td>58.4±12.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>81 (87.1)</td>
<td>23 (88.5)</td>
<td>58 (86.6)</td>
<td>0.807</td>
</tr>
<tr>
<td>Education, yrs</td>
<td>7.6±5.0</td>
<td>5.4±3.4</td>
<td>8.4±5.3</td>
<td>0.009</td>
</tr>
<tr>
<td>History of smoking, n (%)</td>
<td>26 (28.0)</td>
<td>9 (34.6)</td>
<td>17 (23.4)</td>
<td>0.373</td>
</tr>
<tr>
<td>Alcohol intake, n (%)</td>
<td>9 (9.7)</td>
<td>3 (11.5)</td>
<td>6 (9.0)</td>
<td>0.705</td>
</tr>
<tr>
<td>BMI</td>
<td>28.2±5.1</td>
<td>26.5±6.0</td>
<td>28.8±4.7</td>
<td>0.007</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>13 (14.0)</td>
<td>5 (19.2)</td>
<td>8 (11.9)</td>
<td>0.363</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>196.8±46.9</td>
<td>188.3±47.6</td>
<td>199.7±46.6</td>
<td>0.325</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>125.5±53.8</td>
<td>109.3±42.1</td>
<td>131.0±56.4</td>
<td>0.100</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>44.1±11.4</td>
<td>46.3±9.9</td>
<td>43.4±11.8</td>
<td>0.299</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>140.8±81.0</td>
<td>130.0±83.3</td>
<td>144.5±80.6</td>
<td>0.471</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.9±0.3</td>
<td>1.0±0.3</td>
<td>0.8±0.2</td>
<td>0.066</td>
</tr>
<tr>
<td>Hemoglobin A1c, %</td>
<td>5.8±0.7</td>
<td>5.8±0.4</td>
<td>5.7±0.5</td>
<td>0.513</td>
</tr>
<tr>
<td>Conventional hypertension, n (%)</td>
<td>60 (64.5)</td>
<td>20 (76.9)</td>
<td>40 (57.7)</td>
<td>0.119</td>
</tr>
<tr>
<td>Ambulatory hypertension, n (%)</td>
<td>52 (55.9)</td>
<td>16 (61.5)</td>
<td>36 (53.7)</td>
<td>0.496</td>
</tr>
<tr>
<td>Antihypertensive treatment, n (%)</td>
<td>44 (73.3)</td>
<td>14 (70.0)</td>
<td>30 (75.0)</td>
<td>0.432</td>
</tr>
<tr>
<td>IOP, mmHg</td>
<td>12.7±3.0</td>
<td>13.3±3.6</td>
<td>12.4±2.8</td>
<td>0.199</td>
</tr>
</tbody>
</table>

Proportion of glaucoma diagnosis cases = suspected glaucoma 30 (16.2%); glaucoma 20 (10.8%); and GON 50 (27.0%).

BMI = body mass index; HDL = high-density lipoprotein; GON = glaucomatous optic neuropathy; IOP = intraocular pressure; LDL = low-density lipoprotein.

*Among those 26 individuals with GON, 30 eyes (16.2%) had suspected glaucoma and 20 eyes (10.8%) had glaucoma. A total of 49 eyes (26.6%) were identified as eyes with GON.

1P value of the baseline comparison between individuals with GON and healthy eyes.

The prevalence of individuals with antihypertensive treatment was calculated based on the number of individuals with conventional hypertension.

Table 2. Distribution of Blood Pressure Levels in the Total Population and Between Individuals with Glaucamatus Optic Neuropathy and Individuals with Healthy Eyes

<table>
<thead>
<tr>
<th>Blood Pressure Levels</th>
<th>Total Population (n = 93)</th>
<th>Individuals with Glaucamatus Optic Neuropathy* (n = 26)</th>
<th>Individuals with Healthy Eyes (n = 67)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>141.0±22.8</td>
<td>148.7±26.1</td>
<td>138.0±20.8</td>
<td>0.041</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>76.0±8.3</td>
<td>74.4±10.0</td>
<td>76.6±7.5</td>
<td>0.247</td>
</tr>
<tr>
<td>Ambulatory BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hr BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>122.2±15.0</td>
<td>121.9±17.4</td>
<td>122.3±14.2</td>
<td>0.911</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>70.4±8.5</td>
<td>67.0±8.5</td>
<td>71.8±8.2</td>
<td>0.014</td>
</tr>
<tr>
<td>Daytime BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>123.7±14.2</td>
<td>124.1±17.1</td>
<td>123.5±13.1</td>
<td>0.847</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>72.1±8.5</td>
<td>69.3±8.9</td>
<td>73.1±8.2</td>
<td>0.053</td>
</tr>
<tr>
<td>Nighttime BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>118.0±18.6</td>
<td>116.8±20.5</td>
<td>118.4±18.0</td>
<td>0.722</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>66.0±10.0</td>
<td>61.7±9.8</td>
<td>67.6±9.6</td>
<td>0.009</td>
</tr>
</tbody>
</table>

BP = blood pressure.

*P value of the BP comparison between individuals with glaucomatous and healthy eyes.
glaucomatous damage than 1-time measurements of office BP. Previous studies similarly found that ABPM is a reliable predictor of hypertensive retinopathy, diabetic retinopathy, macular alterations, VF defects, and glaucoma.26–28 ABPM is also a better predictor of risk to other organs,29,30 including chronic kidney disease, stroke, and cardiac events.29,32 However, our study is the first to compare ABPM and office BP as indicators of glaucoma risk in the general population, and it suggests that measures from ABPM can be considered as a useful tool for clinicians to identify at-risk individuals long before symptoms of glaucomatous damage appear.

Intraocular pressure was not found to be a risk factor for GON in our study. The role of IOP as a risk factor for

Table 3. Multivariate Logistic Regression Analysis Using the General Estimating Equation to Determine the Association Between Blood Pressure Levels and Glaucomatous Optic Neuropathy

<table>
<thead>
<tr>
<th>Office and Ambulatory BP</th>
<th>Adjusted*</th>
<th>P Value</th>
<th>Fully Adjusted†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td></td>
<td>OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Conventional BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.00 (0.98–1.02)</td>
<td>0.831</td>
<td>1.00 (0.98–1.02)</td>
<td>0.913</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.98 (0.92–1.06)</td>
<td>0.652</td>
<td>0.99 (0.92–1.06)</td>
<td>0.724</td>
</tr>
<tr>
<td>Ambulatory BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hr BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.99 (0.96–1.02)</td>
<td>0.390</td>
<td>0.99 (0.96–1.02)</td>
<td>0.541</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.96 (0.89–1.02)</td>
<td>0.192</td>
<td>0.96 (0.90–1.03)</td>
<td>0.221</td>
</tr>
<tr>
<td>Daytime BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.99 (0.96–1.03)</td>
<td>0.674</td>
<td>1.00 (0.96–1.03)</td>
<td>0.858</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.98 (0.92–1.04)</td>
<td>0.425</td>
<td>0.98 (0.92–1.04)</td>
<td>0.490</td>
</tr>
<tr>
<td>Nighttime BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.98 (0.95–1.01)</td>
<td>0.221</td>
<td>0.99 (0.96–1.01)</td>
<td>0.305</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.95 (0.89–1.01)</td>
<td>0.089</td>
<td>0.95 (0.89–1.01)</td>
<td>0.101</td>
</tr>
</tbody>
</table>

BP = blood pressure; CI = confidence interval; OR = odds ratio.
*Model adjusted by age.
†Fully adjusted, was performed by age, education, BMI, creatinine, refractive error, and IOP.

Figure 1. Proportion of dipper status in healthy and glaucomatous eyes. BP = blood pressure.
Table 4. Multivariate Logistic Regression Analysis Using the General Estimating Equation to Determine the Association Between Dipper Status and Glaucomatous Optic Neuropathy

<table>
<thead>
<tr>
<th>Dipper Status</th>
<th>Value OR (95% CI)</th>
<th>Value P Value</th>
<th>Adjusted*</th>
<th>Fully Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic dipper status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme dipper</td>
<td>9.44 (1.70–52.2)</td>
<td>0.010</td>
<td>19.78 (2.23–175.50)</td>
<td>0.007</td>
</tr>
<tr>
<td>Dipper</td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Nondipper and reverse dipper</td>
<td>0.63 (0.21–1.90)</td>
<td>0.411</td>
<td>1.62 (0.50–5.54)</td>
<td>0.446</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic dipper status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme dipper</td>
<td>4.64 (1.34–16.1)</td>
<td>0.016</td>
<td>5.55 (1.04–29.62)</td>
<td>0.045</td>
</tr>
<tr>
<td>Dipper</td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Nondipper and reverse dipper</td>
<td>1.02 (0.30–3.38)</td>
<td>0.980</td>
<td>0.90 (0.30–3.01)</td>
<td>0.860</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio.

*Model adjusted by age.
†Dipper status follows the definition of Fagard et al., in which night/day BP ratios ≥0.8 indicated reverse dipper, >0.8 to 0.9 indicated dipper, >0.9 to 1.0 indicated nondipper, and >1.0 indicated reverse dipper.

glaucoma in normotensive eyes is well established. Specifically, studies have attributed IOP to the progression of glaucomatous damage (as VF defect progression or increased cup/disc ratio). Given we were unable to follow up, we could not establish whether IOP is related to progression of GON in our study. However, in contrast with other population-based studies, our IOP average (12.7±3.0 mmHg for total population; 13.3±3.6 for GON; and 12.4±2.8 for healthy eyes) is lower; 14.4±3.5 mmHg, 14.6±3.1 mmHg, 14.7±2.4 mmHg, respectively (among individuals 40–49 years of age). The discrete difference of IOP between our sample and other studies might not provide a reliable explanation supporting that IOP is not a risk factor in our population; however, there is evidence suggesting that the relationship between IOP and GON is astonishingly weak, especially at the lower end of IOP levels, indicating that other risk factors are involved in GON. Extrapolating that argument, our mean IOP is nearer to the lower limit of IOP (10 mmHg) than the average mean of the other studies. Thus, we suggest that IOP has less impact on GON in our population sample than in other population-based studies.

The main limitation of the study is the small sample size that precludes us from comparing extreme dipper status as a risk factor for glaucomatous damage in individuals with normal versus low average nighttime BP and from comparing the risk of individuals exhibiting nondipper and reverse dipper status versus dippers. In addition, the combined analyses of glaucoma and suspected glaucoma might hinder specific associations related to glaucoma. However, there is sufficient overlap between suspected glaucoma and early glaucoma to suggest that their shared elements are substantial and worth detecting. Another aspect that needs to be clarified is whether risk factors for extreme dipper status, such as physical activity, sleep quantity and quality, and timing of antihypertensive medications, are more closely associated with GON than extreme dipper status. Last, although we measured conventional BP in a sitting position, we were not able to control the positional changes during ABPM recordings. This note is relevant because positional changes are linked with changes in BP levels. We hope to examine that issue in the future.

In summary, our results support the hypothesis that the association between nocturnal hypotension and GON is determined by having an extreme dipping effect and not by low average nighttime BP levels. Further studies examining the progression to glaucoma in individuals identified as high risk would clarify the usefulness of extreme dipper status as a risk factor. Our results support the use of ABPM to help identify individuals with extreme dipper status who are at high risk of GON and who should undergo further ophthalmological assessment. Therapies that modify glaucoma risk are urgently needed, and new approaches to avoiding the extreme dipper effect, such as changes in the timing of antihypertensive drug intake, might be effective.

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References

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Abbreviations and Acronyms:
ABPM = ambulatory blood pressure monitoring; BMI = body mass index; BP = blood pressure; GEE = generalized estimating equations; GON = glaucomatous optic neuropathy; IOP = intraocular pressure; LDL = low-density lipoprotein; MAS = Maracaibo Aging Study; RNFL = retinal nerve fiber layer; SD = spectral domain; VF = visual field.

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