Relative Change in Diurnal Mean Ocular Perfusion Pressure: A Risk Factor for the Diagnosis of Primary Open-Angle Glaucoma

Mitra Sehi,1 John G. Flanagan,1,2 Letlei Zeng,3 Richard J. Cook,5 and Graham E. Trope2

PURPOSE. To investigate diurnal change and pattern of variation in intraocular pressure (IOP) and systolic (SBP) and diastolic (DBP) blood pressures in a group with untreated primary open-angle glaucoma (uPOAG) and compare it with an age-matched, normal group.

METHODS. IOP, SBP, and DBP were measured in 14 patients with uPOAG and in 14 normal subjects, every hour between 7 AM and 10 PM and the mean ocular perfusion pressure (MOPP) was calculated. Mixed-effect linear models were used to analyze the repeated-measures data in which both fixed and random effects were included. The relative diurnal change was calculated as the percentage decrease from maximum.

RESULTS. The uPOAG group had the higher IOP (P < 0.001) and lower MOPP (P = 0.025). There was a significant diurnal change in IOP, SBP, DBP, and MOPP in both groups (P < 0.001). The pattern of diurnal variation in IOP (P = 0.137), SBP (P = 0.569), and DBP (P = 0.957) was not significantly different between groups but was significantly different for MOPP (P = 0.040). MOPP and IOP were most similar at 7 AM and 1 PM. Postprandial hypotension was significant for SBP, DBP, and MOPP (P < 0.001), but not IOP (P = 0.388) in both groups. The relative change in MOPP was larger in the uPOAG group (58% vs. 26%, P < 0.001), but the change in IOP was similar (42% vs. 41%, P = 0.786). There was a significant effect of DBP on IOP over the course of the day in the uPOAG group (P = 0.011) but not in the normal group (P = 0.735).

CONCLUSIONS. The relative diurnal change in IOP was similar in both uPOAG and normal subjects but MOPP showed a significant difference. MOPP significantly decreased after lunch, and was at its lowest in uPOAG at 7 AM, when IOP was at its highest. A significant association was found between diurnal DBP and IOP in uPOAG. (Invest Ophthalmol Vis Sci. 2005;46: 561–567) DOI:10.1167/iovs.04-1033

I t has been proposed that vascular risk factors are among the major precipitating factors that lead to the development of glaucomatous optic neuropathy.1–5 Blood flow in any tissue is generated by the perfusion pressure that is defined as the difference between mean arterial blood pressure (MAP) and venous pressure. In the resting position, MAP is calculated as

\[
MAP = DBP + \frac{1}{3}(SBP - DBP)
\]

where the difference between the systolic (SBP) and diastolic (DBP) blood pressures is the pulse pressure.11 In the eye, the venous pressure should be marginally higher than the intraocular pressure (IOP), to allow for adequate blood circulation. Therefore, for the calculation of the mean ocular perfusion pressure (MOPP), IOP is substituted for venous pressure5,12–13 so that the MOPP in the the eye is equal to the difference between the MAP and IOP.14–16

\[
MOPP = \frac{2}{3}(DBP + \frac{1}{3}(SBP - DBP)) - IOP
\]

The perfusion pressure changes during the day, but the tissue blood flow should remain stable, to maintain metabolic activity.11,17–19 Diurnal variation of IOP has been well documented,20–29 and it has been demonstrated that the range of IOP fluctuation is larger than normal in persons with untreated glaucoma (Heijl A, et al. IOVS 2004;45:ARVO E-Abstract 943).20,23–25,27–29,32 Zeimer.33 hypothesized that if the diurnal variation in IOP were a pure biorhythm, it could be described by a cosine function, in which the higher the IOP, the higher the amplitude and therefore the greater the diurnal change.35,36 Recently, doubts have been raised about the idea that a large diurnal range of IOP is an independent risk factor for the development of glaucoma. Sacca et al.32 studied diurnal fluctuations of IOP in three groups—primary open-angle glaucoma (POAG), low-tension glaucoma, and normal—and found that the daily IOP fluctuations were directly proportional to the level of IOP. Heijl and Bengtsson (IOVS 2004;45:ARVO E-Abstract 943) demonstrated that in a group of patients who participated in a 10-year study of ocular hypertension, the higher the IOP, the larger the range of diurnal variation, and that diurnal variation in IOP was not an independent risk factor for development of glaucoma. However, mean IOP was found to be a strong risk factor.

Diurnal variation of SBP has also been well studied (Sehi M, et al. IOVS 2004;45:ARVO E-Abstract 4447; Sehi M, et al. IOVS 2003;44:ARVO E-Abstract 979).22,28,35–41 However, there are few studies regarding diurnal variation in MOPP46–42 and its role as a risk factor for the diagnosis of POAG.

The purpose of this study was to investigate the diurnal change and diurnal pattern of variation in IOP, SBP, and MOPP in a group of patients with newly diagnosed, early POAG, before treatment was begun, and to compare the results with those in a group of healthy, age-matched volunteers.

METHODS

This study was of a prospective cohort design. The sample consisted of two groups, patients with untreated (u)POAG and healthy, age-
matched volunteers. Participants were recruited from clinics at the University of Waterloo and four private ophthalmology/optometry offices in the Waterloo region. Volunteers were excluded from the study if they had a history of systemic or ocular disease that would affect systemic or ocular blood flow, had taken medication that would affect the blood pressure or blood flow, had a central nervous system (CNS) disease, or had taken any prescribed medication for CNS disease affecting systemic or ocular blood flow, had taken medication that would affect the blood pressure or blood flow, had a central nervous system (CNS) disease, or had taken any prescribed medication for CNS disease within the previous 6 months or if they were smokers.

Participants were eligible for entry into the uPOAG group if they were at least 35 years old. SBP was within the range of 90 to 139 mm Hg and resting DBP was < 89 mm Hg, and IOP was > 21 mm Hg and if they had received a diagnosis of POAG but had not started treatment. The diagnosis of POAG was made by a single glaucoma specialist (GET).

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Participants were eligible for entry into the normal group if SBP was within normal limits, and there was no sign of optic neuropathy. Normal volunteers were age matched to the uPOAG group.

Ethics approval was granted by the Office of Research at the University of Waterloo. All procedures conformed to the Declaration of Helsinki. Informed consent was obtained from each volunteer after explanation of the nature and possible consequences of the study. All volunteers avoided activities that could increase the blood pressure or heart rate, such as climbing stairs. Meals were provided at 12:30 and 6:30 PM but did not include alcohol, tea, coffee, or additional salt. Volunteers drank one cup of tea or coffee between 9 and 10 AM. One investigator (MS) completed all measurements. Blood pressure was measured with a brachial mercurial sphygmomanometer on the left arm after the subject had been seated for at least 5 minutes. The IOP and SBP were measured every hour between 7 AM and 10 PM during a single 1-day session. The assessment of IOP was performed with a slit-lamp–mounted Goldmann applanation tonometer. Central corneal thickness (CCT) was measured once in the midmorning with an ultrasound pachymeter (DGH-550 Pachette 2; DGH Technology, Inc., Exton, PA). IOP was adjusted 3 mmHg for every 50 µm that the corneal thickness deviated from an average of 535 µm. The ocular perfusion pressure was calculated as the difference between two thirds of the MAP and IOP. In the glaucoma group, the eye with stronger evidence of glaucoma was selected for participation in the study. In the normal group, the test eye was selected randomly.

Analysis for repeated-measures data was conducted to characterize diurnal variation by using mixed-effect linear models that include both fixed and random effects. Coefficients of explanatory variables were treated as fixed effects, as in standard linear models, and the intercept was treated as a random effect, to accommodate correlations in the responses within patients over assessments. The explanatory variables considered included time, an indicator of whether a participant was normal or a patient with uPOAG (disease variable), and the associated interactions (time and disease). The explanatory variables were selected to provide insight into patterns of diurnal variation in ocular perfusion pressures in both normal and patients with uPOAG.

Absolute and relative diurnal changes for each outcome measure were calculated. The absolute diurnal change—the difference between maximum and minimum values (range)—was determined for each individual, and the average was calculated for each group. The relative diurnal change—the percentage decrease from maximum (or range divided by maximum)—was determined for each individual, and the average was calculated for each group. The between-group comparisons were analyzed using unpaired two-tailed Student’s t-test.

The association between SBP and IOP was also examined by using mixed-effect linear models. IOP was considered to be the response of interest, and the explanatory variables included patient group, time, SBP, and DBP and the interaction between the last three variables and patient group.

RESULTS

Fourteen volunteers with uPOAG (mean age, 56.3 ± 12 years; 7 women) and 14 healthy age-matched volunteers (mean age, 57.6 ± 9.9 years; 9 women) were examined. All 28 volunteers were white.

There was a significant diurnal change in IOP in both the uPOAG and normal groups compared to the 7 AM baseline (P < 0.001; Fig. 1). The mean IOP was significantly higher in patients with uPOAG than in normal subjects throughout the day (19.2 and 13.0 mm Hg, respectively; P < 0.001; Table 1). The absolute diurnal change was greater in the uPOAG group (10.3 ± 2.2 mm Hg, uPOAG; and 6.4 ± 1.4 mm Hg, normal; P < 0.001). The maximum IOP for both groups was recorded at 7 AM (9/14 uPOAG, 8/14 normal subjects), with the uPOAG group mean IOP being significantly higher (by 7.9 mm Hg; P < 0.001). The pattern of diurnal variation in IOP relative to the 7 AM value was not significantly different between patients with uPOAG and normal subjects (time and disease interaction; P = 0.137). In summary, there was a significant diurnal change in IOP in both groups, but the pattern of diurnal variation was similar in both groups.

Table 1. Diurnal Pressures

<table>
<thead>
<tr>
<th></th>
<th>IOP</th>
<th>SBP</th>
<th>DBP</th>
<th>MOPP</th>
<th>MOPP-IOP</th>
</tr>
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<tbody>
<tr>
<td>POAG</td>
<td>19.2 ± 5.0</td>
<td>128.6 ± 11.3</td>
<td>73.6 ± 8.4</td>
<td>42.0 ± 7.1</td>
<td>22.7 ± 11.0</td>
</tr>
<tr>
<td>NORMALS</td>
<td>13.0 ± 3.0</td>
<td>125.9 ± 13.6</td>
<td>73.4 ± 6.9</td>
<td>47.6 ± 6.1</td>
<td>34.7 ± 7.9</td>
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</table>

Data are expressed as the mean ± SD.
There was a significant diurnal change in SBP in both the uPOAG and normal groups compared with the level at 7 AM ($P < 0.001$; Fig. 2). The mean SBP was not significantly different between the two groups (Table 1; $P = 0.543$) throughout the day. There was a significant increase in SBP from 4 PM when compared with that at 7 AM, for both groups; however, the pattern of diurnal variation was not significantly different between groups (time and disease interaction; $P = 0.233$).

There was a significant diurnal change in DBP in both the uPOAG and normal groups compared with the 7 AM reading ($P < 0.001$; Fig. 3). The mean DBP was not significantly different between the two groups (Table 1; $P = 0.954$) throughout the day. The pattern of diurnal variation was comparable for uPOAG and normal groups (time and disease interaction; $P = 0.550$).

There was a significant diurnal change in MOPP in both the uPOAG and normal groups compared with that at 7 AM ($P < 0.001$; Fig. 4). The mean MOPP was significantly lower in patients with uPOAG than in normal subjects (42.0 and 47.6 mm Hg, respectively; $P = 0.024$; Table 1) throughout the day, and the absolute diurnal change was greater in the uPOAG group (19.2 ± 3.8 mm Hg uPOAG; 14.4 ± 3.2 mm Hg normal; $P = 0.001$). The minimum MOPP in the uPOAG group was recorded at 7 AM (mean 35.5 mm Hg), and it was significantly lower than normal subjects at this time (8.8 mm Hg; $P = 0.003$). The pattern of diurnal variation in MOPP relative to the 7 AM level was significantly different between patients with uPOAG and normal subjects (time and disease interaction; $P = 0.040$). Specifically, the MOPP was elevated at 2 PM and at the end of the day (from 8 PM) in the uPOAG group, but in the normal group there was only a slight increase. In summary, there was a significant diurnal change in MOPP in both groups, and the pattern of diurnal variation was different between groups.

There was significant postprandial hypotension in SBP ($P < 0.003$) and DBP ($P < 0.001$). We also found a significant postprandial hypotension in MOPP ($P < 0.001$) in both groups. IOP showed no significant change in either group after lunch ($P = 0.642$ uPOAG; $P = 0.069$ normal).

The percentage decrease (relative change) in IOP was similar between patients with uPOAG and normal subjects (42% and 41%, respectively; $P = 0.786$). We did not find any significant difference between the percentage decrease in SBP (20% and 19.6%, respectively, $P = 0.878$) or DBP (24%, 21%, $P = 0.263$) in either group. When we compared the percentage decrease in MOPP, we found a significant difference between uPOAG and normal subjects (38% and 26%, respectively, $P < 0.001$). There was no correlation between the change in SBP...
and the change in IOP for the uPOAG group, during the course of the day \( (P = 0.736) \). However, the change in DBP had a significant effect on IOP \( (P = 0.011) \) such that for every 1 mm Hg increase in DBP, the IOP increased 0.086 mm Hg. In the normal group, neither SBP \( (P = 0.585) \) nor DBP \( (P = 0.733) \) had a significant effect on IOP over the course of the day.

**DISCUSSION**

In patients with untreated glaucoma, the diurnal change in IOP has been reported to be between 4.8 and 18.4 mm Hg,\(^{46,47}\) whereas, in the normal eyes, it has been reported to be between 2.8 and 6.5 mm Hg.\(^{48,49}\) Our uPOAG group fell within this range, with an average diurnal change in IOP of 10.3 ± 2.8 mm Hg after correcting for corneal thickness (9.75 ± 2.8 mm Hg before correcting for corneal thickness). However, our normal group had an average diurnal change in IOP of 6.8 ± 1.4 mm Hg, slightly higher than previously reported normal IOP, after correcting for corneal thickness (6.75 ± 1.5 mm Hg before correcting for CCT). Interstudy comparisons are difficult, because study designs are frequently different—for example, in terms of gender distribution,\(^{50,51}\) age group,\(^{30}\) race,\(^{32,55}\) type of tonometer,\(^{20,49,54-60}\) frequency of measurement and starting time,\(^{21,27,61-65}\) corneal thickness considerations,\(^{52,64-69}\) and the calculation of the diurnal change (Heijl A, et al. \textit{IOVS} 2004;45:ARVO E-Abstract 943).\(^{20,26,27,29,42,48,54,55,60,62,63,71-74}\) In many of these studies, the diurnal change was calculated by using the maximum and minimum of the group mean IOP at each measurement time, rather than the average of the individual diurnal changes in IOP that we used. Our method of calculating diurnal change was consistent with that used by Heijl and Bengtsson (\textit{IOVS} 2004;45:ARVO E-Abstract 943). However, if we calculate the diurnal change using the alternate method, our results would be 6.5 mm Hg for the uPOAG group and 4.1 mm Hg for the normal group, well within the previously reported ranges.

Postprandial systemic hypotension is a well-known phenomenon.\(^{39,40,41,75}\) The impact of postprandial reduction of cerebral perfusion has also been reported.\(^{75-78}\) However, to the best of our knowledge, this is the first report of postprandial reduction in ocular perfusion pressure in both patients with uPOAG and normal volunteers. It is uncertain why the decline of MOPP was not significant after the evening meal. We did not study the association between the level of MOPP decrease and the meal size, but an association has been reported in the past between blood pressure and meal size.\(^{79-81}\)

It has been reported that as IOP increases, the eye maintains perfusion until the IOP is 6 mm Hg below the ocular perfusion pressure.\(^{16,82-84}\) Figure 5 shows the diurnal profile of IOP and MOPP in a patient with an asymmetric presentation of glaucoma. It has been suggested that large diurnal variation in IOP is an independent risk factor for the development of glaucoma.\(^{20,24,29,70,85}\) In our study, although the absolute diurnal change in IOP was different between patients with uPOAG and normal subjects, we found that the relative diurnal change in IOP, expressed as a percentage of the maximum level, was similar between uPOAG and age-matched normal subjects. These results agree with Zeimer’s hypothesis\(^{33}\) and the studies of Heijl and Bengtsson (\textit{IOVS} 2004;45:ARVO E-Abstract 943) and Sacca et al.,\(^{32}\) who found that the daily IOP fluctuations were directly proportional to IOP level. They suggested that diurnal variation in IOP was therefore not an independent risk factor for development of glaucoma. Our results agree with

**Table 2. The Absolute and Percentage Diurnal Changes in IOP and MOPP**

<table>
<thead>
<tr>
<th></th>
<th>IOP Change (Absolute)</th>
<th>IOP Change (Relative, %)</th>
<th>MOPP Change (Absolute)</th>
<th>MOPP Change (Relative, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>uPOAG</td>
<td>10.3 ± 2.8</td>
<td>42 ± 11</td>
<td>19.2 ± 3.8</td>
<td>38 ± 7</td>
</tr>
<tr>
<td>Normals</td>
<td>6.8 ± 1.4</td>
<td>41 ± 7</td>
<td>14.4 ± 3.2</td>
<td>26 ± 5</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SD.
these previous studies and also suggest that diurnal IOP should not be considered a risk factor for the diagnosis of POAG.

We found that the percentage decrease in MOPP was significantly different between uPOAG and age-matched normal subjects. The mixed-effect linear model supported these findings, as the pattern of diurnal variation in MOPP was significantly different between patients with uPOAG and normal subjects. The difference between groups is somewhat exaggerated in the MOPP diurnal curve, due to the cumulative effect of a higher IOP and lower BP. This was particularly noticeable at 7 AM in the uPOAG group.

Our findings suggest that the absolute diurnal measures of IOP alone are of limited clinical value in the diagnosis of POAG, but should be considered in conjunction with measures of diurnal systemic BP. We propose that the relative diurnal change in MOPP be considered a risk factor for the diagnosis of POAG. Our results also revive the debate with respect to the impact of treatment for systemic hypertension in patients with glaucoma—that is, a reduction in DBP of 12.5 mm Hg or in SBP of 25 mm Hg has the same impact on MOPP as an increase in IOP of 5 mm Hg.

A positive correlation between SBP and IOP has been reported in patients with glaucoma.1,2,6,7,36–39 We found no difference between the uPOAG and normal groups in the level of SBP and DBP, but there was a significant association between diurnal variation in DBP and IOP in patients with uPOAG, such that a 1-mm Hg increase in DBP was associated with a 0.09 mm Hg increase in IOP. It is important to clarify that our results do not suggest a simple relationship between hypertension and IOP, as all our participants had normal blood pressure. Our results indicate that there was a significant effect of DBP on IOP over the course of the day in patients with uPOAG that was not apparent in normal subjects. This does not imply that the association is causative, as it is most likely an indication of vascular dysfunction in the uPOAG group.

In conclusion, the relative change in diurnal MOPP distinguished patients with uPOAG from normal subjects, but the relative change in IOP was not. The assessment of MOPP may be a useful clinical tool for the diagnosis of early glaucoma. Change in DBP had a significant effect on IOP over the course of the day. There was postprandial hypotension in MOPP in both groups, which should be considered when evaluating ocular perfusion. MOPP was at its lowest in uPOAG at 7 AM when IOP was at its highest. The effect of periods of reduced ocular perfusion pressure on optic nerve head blood flow remains to be answered. Such studies are ongoing in our laboratory.

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