Anterior Optic Nerve Capillary Blood Flow Response to Diurnal Variation of Mean Ocular Perfusion Pressure in Early Untreated Primary Open-Angle Glaucoma

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PURPOSE. To examine the impact of diurnal variation in intracocular pressure (IOP) and mean ocular perfusion pressure (MOPP) on the variation in anterior optic nerve capillary blood flow (BF) in patients with untreated early primary open-angle glaucoma (uPOAG) and healthy volunteers.

METHODS. Fourteen patients with uPOAG (age, 56.3 ± 12 years [SD]; seven men) and 14 normal subjects (age, 57.6 ± 9.9 years; five men) were examined. Diurnal IOP, systolic (SBP) and diastolic (DBP) blood pressures, and optic nerve head (ONH) topography were measured every hour; and diurnal BF was measured by flowmeter every 2 hours between 0700 and 2200 hours. A perfusion image analyzer was used to calculate the mean BF within the rim (mean rim flow, MRF). The local flow (LF) was calculated using the median and mean flow rates within a 10 × 10-pixel window placed on the rim in the area of maximum topography fluctuation (MTF). The MOPP was then calculated. Mixed-effect linear models were used to analyze the repeated measures data in which both fixed and random effects were included.

RESULTS. IOP, BP, and MOPP had significant diurnal variation (P < 0.040). LF measured at the sector of MTF significantly changed in patients with uPOAG (P = 0.006) but not in normal subjects (P = 0.660). MRF did not show significant diurnal change in either group (P = 0.130, P = 0.770). LF increased significantly after lunch in the uPOAG group (P = 0.001). SBP had a significant effect on LF over the course of the day in the uPOAG group (P = 0.045). The diurnal change in IOP, BP, and MOPP did not have a significant effect on MRF in either group. In uPOAG, the local flow, in areas of greatest topographical change, correlated inversely with IOP at 0700 hours (P ≤ 0.002).

CONCLUSIONS. The mean rim flow did not change during the day, implying that the anterior optic nerve capillary blood flow was autoregulated in both normal subjects and in patients with uPOAG, despite significant changes in IOP and MOPP. However, the regions of greatest diurnal change in rim topography (MTF) had significant diurnal change in capillary blood flow in patients with uPOAG but not in normal subjects. (Invest Ophtalmol Vis Sci. 2005;46:4581–4587) DOI:10.1167/iovs.05-0209

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Many studies have demonstrated altered ocular blood flow (BF) in patients with glaucoma.1-19 The mean ocular perfusion pressure (MOPP) is the pressure that forces blood to flow through the ocular vascular bed and is equal to the difference between the mean arterial pressure (MAP) and the venous pressure at the exit point. The venous pressure in the eye is approximately equal to the intraocular pressure (IOP).20,21 When the perfusion pressure changes, tissue BF is autoregulated.22 Autoregulation is the physiologic phenomenon in which the local arteriolar resistance changes dynamically to keep tissue BF at a relatively constant level that is determined by the local metabolic activity, despite changes in MAP and perfusion pressure.23,24,25 Under physiological conditions when the perfusion pressure is low, the resistance of the lumen of the vein is reduced to maintain the BF at a constant rate.26 If the IOP exceeds the orbital venous pressure, the local arteriolar resistance changes, to stabilize and regulate the BF. However, there is a limit to the extent that the terminal arterioles can change the resistance.24 Therefore, autoregulation operates within a critical range of perfusion pressure.24,25 Blood flow autoregulation of the monkey optic nerve head has been reported to break down when the perfusion pressure is below 50 mm Hg.24,26,27 The BF of the human optic nerve head starts to decline when the IOP reaches 45 mm Hg. However, it is not clear to what extent low blood pressure (BP) or low perfusion pressure is a risk factor, per se, in the development of glaucoma and whether autoregulation at the optic nerve head (ONH) can fully compensate for low perfusion pressure.

The ONH BF depends on the balance between the perfusion pressure and IOP and also the resistance to flow. Diurnal variations of IOP and systemic blood pressure (BP) have been well documented (Sehi M, et al. IOVS 2003;44:ARVO E-Abstract 979).28-30 There have also been studies regarding the diurnal variation of MOPP.39-42 The autoregulation of the optic nerve has also been demonstrated.25,43,44 However, there are not many human studies regarding the ONH BF response to these diurnal variations (Sehi M, et al. IOVS 2003;44:ARVO E-Abstract 979; Sehi M, et al. IOVS 2004;45:ARVO E-Abstract 4447).59,41 It is also unclear whether the autoregulatory response of the ONH BF to the diurnal variation of MOPP is the same in all locations of the neuroretinal rim, as Cioffi et al. demonstrated in a nonhuman primate model, that chronic ischemia causes significant loss of optic nerve axons that often clusters within specific quadrants. The varying regional susceptibility may result from local differences in vasculature, anatomy, metabolism or autoregulation of the ONH.

The purpose of this study was to investigate the anterior optic nerve capillary BF response to diurnal variation of IOP and MOPP in patients with untreated early primary open-angle glaucoma (uPOAG) and healthy volunteers.

METHODS. Two groups of volunteers were recruited into this prospective cohort study, as previously described.12 The inclusion criteria common to...
both groups were as follows: Participants were eligible for entry into the study if they were at least 35 years of age; their resting SBP was 90 to 139 mm Hg, and their resting DBP was ≤89 mm Hg; they did not have any history of systemic or ocular disease that would intervene in the regular systemic or ocular BF (e.g., diabetes, cardiovascular disorders, hyper- or hypothyroidism, or glaucoma); they had not taken any prescribed medication for hypertension, hypotension, or increasing BF or blood thinners within the past 6 months; they had not taken any prescribed medication for central nervous system (CNS) diseases within the past 6 months (e.g., antiepilepsy drugs, antidepressant drugs); they had not taken any over-the-counter medications that would intervene in the regulation of BF or BP; they were nonsmokers; and they were willing and able to comply with the study protocol and to sign an informed consent.

Participants were eligible for entry into the uPOAG group if the IOP was >21 mm Hg at sometime during the day, they had optic neuropathy consistent with a diagnosis of glaucoma, and they had not started glaucoma treatment.

This group of patients with glaucoma were said to have early POAG because an abnormal visual field was not a criterion for the diagnosis of glaucoma. The visual field defects were at early stages, as the mean deviation (MD) in the uPOAG group was −1.5 ± 1.4 db. A diagnosis of open-angle glaucoma was made if the anterior chamber angle was open together with signs of glaucomatous optic neuropathy and/or a nerve fiber layer defect. Disc and nerve fiber layer disease, such as a disc hemorrhage, nerve fiber layer slit and wedge defects, and signs of optic neuropathy such as asymmetrical cupping, generalized enlargement or vertical enlargement of cupping, neuroretinal rim tissue loss and focal notching, were considered in the diagnosis of POAG. Also large diurnal IOP fluctuations (>6 mm Hg) were considered abnormal. The diagnosis of POAG was made by a single glaucoma specialist (GET).

Participants were eligible for entry into the normal group if their IOP was ≤21 mm Hg, the Glaucoma Hemifield Test (Humphrey Field Analyzer, Carl Zeiss Meditec, Inc., Dublin CA) categorized the visual field results as being within normal limits, and there was no sign of optic neuropathy.

All procedures of the experiment were approved by the Office of Human Research at the University of Waterloo and were in agreement with the provisions of the Declaration of Helsinki. Volunteers signed the approved consent form after the procedures and their possible consequences were explained to them in detail. After the agreement, they participated in a preliminary visit. All preliminary and diurnal measurements including determination of the ONH BF and topography were completed by one investigator (MS).

At the preliminary visit, participants completed questionnaires regarding their health status. Blood pressure, IOP, visual acuity, and refractive error were determined. Heidelberg Retina Tomography I (HRT I; Heidelberg Engineering GmbH, Heidelberg, Germany) images were acquired, and the profile maps were used to determine the dioptric difference between regions of the ONH and the peripapillary retinal surface and to find the best dioptric foci for the areas of interest on the neuroretinal rim to measure accurately the ONH capillary BF using the Heidelberg Retina Flowmeter (HRF; Heidelberg Engineering GmbH).

The HRF is a scanning laser Doppler flowmeter that combines laser Doppler techniques with a scanning laser system to estimate the ocular capillary BF.40–50 A coherent infrared laser that is focused on an area of interest in the back of the eye undergoes a frequency shift when striking moving red blood cells. The surrounding tissue reflects the original frequency. The interference of these two reflected frequencies creates a beat. The frequency of the beat equals the Doppler frequency shift.51 The scanned area is composed of 64 lines, each of which is scanned 128 times. A digitizer converts the received beat to a digital signal, so that each line is composed of 256 pixels. For pixels, fast Fourier transforms (FFT) convert 128 measurements of the intensity (as a function of time) to the power spectrum (as a function of frequency). Volume, flow, and velocity are calculated based on this power spec-
BF for both normal subjects and patients with uPOAG. Patient-disease (disease variable), and the associated interactions (time and considered included time, whether a participant was normal or had responses within patients over assessments. The explanatory variables treated as fixed effects, as in standard linear models, and the intercept measures were analyzed with mixed-effect linear models for the HRF images accurately when analyzing them with the AFFPIA software.

After data extraction, diurnal variation of flow and various pressures measured were analyzed with mixed-effect linear models for the repeated-measures data. 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, whether a participant was normal or had uPOAG (disease variable), and the associated interactions (time and disease). The explanatory variables were selected to provide insight into patterns of diurnal variation in IOP, ocular perfusion pressure, and BF for both normal subjects and patients with uPOAG. Patientspecific characteristics were considered in these models. The association between IOP and MOPP and flow at 0700 hours was also examined in each group, by using the Pearson product moment correlation coefficient.

The mean BF within the neuroretinal rim (mean rim flow, MRF) was measured with the automatic full-field perfusion image analyzer (AFFPIA). The area of cupping defined in HRT images was applied as a guide to reproduce the size and the location of the cupping on the HRF images accurately when analyzing them with the AFFPIA software.

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untreated POAG 

untreated POAG (without the outlier) 

normal subjects 

Data are expressed as the mean ± (SD) (range).

0.006, respectively); however, the normal group did not (P = 0.454; P = 0.658). The minimum median and mean LFs for the uPOAG group was before lunch at 1100 hours (median, 133.6 AU ± 85.1; mean, 236.8 ± 97.7 AU) and the maximum was at 1300 hours after lunch (median, 241.8 ± 114.7 AU; mean, 325.5 ± 115.0 AU). The minimum median and mean LFs for the normal group was after lunch at 1300 hours (median, 197.7 ± 127.4 AU; mean, 318.7 ± 153.7 AU). The pattern of diurnal variation in median and mean LFs during the day was significantly different between uPOAG and normal subjects (time and disease interaction; P < 0.010).

The MRF was not significantly different between the two groups at 0700 hours (219.3 ± 104.6 AU in uPOAG, 254.0 ± 81.8 AU in normal subjects, P = 0.598; Fig. 3) and throughout the day (224.99 ± 94.5 AU in uPOAG, 239.88 ± 48.1 AU in normal subjects, P = 0.585). Neither of the groups had a significant diurnal change in MRF compared with that at 0700 hours (uPOAG, P = 0.130; normal, P = 0.770). The minimum MRF for the uPOAG group was before lunch at 1100 hours (200.9 ± 100.0 AU) and the maximum was after lunch at 1300 hours (267.2 ± 145.7 AU). There was not a statistically significant difference between the pattern of diurnal variation in MRF during the day between uPOAG and normal subjects (time and disease interaction; P = 0.320).

Compared with 1100 hours, both the median and mean LFs significantly increased after lunch in uPOAG (P < 0.002) but not in normal subjects despite a significant decrease in MOPP at that time. Compared with that at 1100 hours, the MRF significantly increased after lunch in uPOAG (P = 0.004) but not in normal subjects (P = 0.418), although over the course of the day the MRF did not show a significant diurnal change in either group.

The effects of pressures on BF measures were examined during the day in both groups. There was no significant effect of IOP, DBP, or MOPP on the median or mean LFs over the course of the day in either group. The effect of the SBP on the median LF in uPOAG over the course of the day was not significant in either group (P = 0.327 for uPOAG; P = 0.214 for normal subjects). However, the SBP had a significant effect on the mean LF in uPOAG over the course of the day (P = 0.043), so that a 1-mm Hg increase in SBP was associated with a 2.5-AU increase in mean LF. The IOP, DBP, and MOPP had no significant effect on MRF over the course of the day in either group; however, SBP had a significant effect on MRF in normal subjects, so that a 1-mm Hg increase in SBP was associated with a 1.7-mm Hg decrease in the MRF in normal subjects, but not in patients with uPOAG.

The association between IOP and flow at 0700 hours was examined. In uPOAG, the IOP at 0700 hours had a significant inverse correlation with the median LF (r = -0.78, P = 0.001) and the mean LF (r = -0.76, P = 0.002), but not with the MRF (r = -0.36, P = 0.205). In normal subjects, the IOP did not correlate significantly with the median LF (r = 0.22, P = 0.441), mean LF (r = 0.35, P = 0.221), or MRF (r = 0.31, P = 0.276) at 0700 hours. The association between MOPP and flow at 0700 hours was also examined. In uPOAG, the MOPP had a significant direct correlation with the median LF (r = 0.595, P = 0.025). There was no significant association between the MOPP and mean LF (r = 0.449, P = 0.107) or MRF (r = 0.428, P = 0.127) at 0700 hours in uPOAG. In normal subjects, the MOPP at 0700 hours was not significantly correlated to the median LF (r = 0.193, P = 0.509), mean LF (r = 0.053, P = 0.910), or MRF (r = 0.076, P = 0.795).

**Discussion**

It has been demonstrated that interindividual variability of the HRF is higher than the intraindividual variability of this machine. However, Tsang et al. showed that when the HRF is
used to observe the capillary BF in the same eye over time, a meaningful comparison is achieved if the vessel alignment and the intensity of light are controlled properly, to provide a comparable level of noise between images. In our study, we carefully controlled for accurate alignment of vessels and the intensity of light. We also used each patient’s flow data as his/her own reference, to study intrapatient diurnal variation of ONH BF. With careful consideration of different dioptic foci (using HRT I maps) for different locations of the ONH, we tried to achieve the closest depth of penetration possible for the area of interest. The mixed-effect model used for the analysis of the flow data respects patient-specific characteristics and its error term adjusts for noise (such as imaging noise) within images.

We found no significant difference between the median/mean LF and MRF of the two groups during the day. This may be explained by the stage of disease, as our volunteers were newly diagnosed and had early disease (mean MD, 1.9 dB). It has previously been reported that rim BF in POAG is lower than in normal subjects. However, it is likely that such observations are dependent on the stage of disease, although Jonas et al. suggested it was difficult to find a clear relationship between disease stage and a decrease in BF.

We found the pattern of diurnal variation in median/mean LF was different between patients with uPOAG and normal subjects. This difference was specifically evident after lunch, particularly in response to reduced MOPP. The median and mean LF remained stable in the normal group and increased in the uPOAG group after lunch (in 12/14 patients with uPOAG). It is unclear why the ONH capillary BF responds to the decreased MOPP by increasing the LF. If the ONH behaved as a passive vascular system, a decrease in the BF would have been expected. The opposite response that we observed could be due to local vasodilatory effects that attempt to compensate for the low perfusion pressure but was exaggerated due to vascular dysregulation in the uPOAG. We found sectors of the ONH in uPOAG that demonstrated both fluctuation in topography and fluctuation in local BF during the day. This suggests that local regulatory mechanisms may change in uPOAG.

Previous studies have shown defects in the microcirculation of the optic disc as small areas of relatively little filling of the small vessels of the disc with fluorescein in primary open-angle glaucoma. Gifford and Sullivan showed in a nonhuman primate model that chronic optic nerve ischemia causes significant loss of optic nerve axons with varying regional susceptibility and that the damaged regions often clusters within specific quadrants. They suggested that localized damage may result from regional differences in anatomy, metabolism, or vasculature of the primate optic nerve. Our findings were also consistent with those of Pillunat et al. and Hafez et al. who suggested that there are sectors of the rim in uPOAG that show significant diurnal change in local flow, and this is a sign of defective autoregulation at some locations on the neuroretinal rim.

The fact that locations that showed fluctuation in topography did not show fluctuation in the BF in normal subjects indicates that, in normal subjects, the mechanisms that regulate the LF are active. However, the exact mechanism responsible for topographic fluctuations is not clear. Currently, we are studying the potential causes of the fluctuation of topography in both uPOAG and normal subjects at our laboratory.

The MRF did not significantly change during the day in either the normal or the uPOAG group compared with that at 0700 hours. There was a momentary increase after lunch in MRF in the uPOAG group; but overall, over the course of the day, the fluctuation of MRF was not significant. This indicates that anterior optic nerve capillary BF behaves as an autoregulated capillary bed as it has been suggested by others, despite significant changes in IOP and MOPP. Sampaolesi et al. suggested that ONH blood supply is regulated by an autoregulation system that acts in normal subjects, in those with hypertensive and preperimetric glucomas, but not in those with advanced glaucoma. Flammer et al. suggested that the hemodynamic alterations may, at least partially, be primarily due to a vascular dysregulation, leading to both low perfusion pressure and insufficient autoregulation. Pillunat et al. found that some disc locations in some individuals do not show autoregulation.

We found that the SBP had a significant positive effect on the mean LF in the uPOAG group over the course of the day. This result is also an indication of an impaired autoregulation at these unstable locations, as the microvasculature in these areas was not able to regulate the LF appropriately. FuchsJager-Mayrl et al. also found an abnormal association between BF and ocular perfusion in patients with POAG.

The topography fluctuated most frequently in the temporal sector for both uPOAG (9/14) and normal subjects (13/14). Overall, a lower BF has been reported in both the temporal neuroretinal rim (Sehi M, et al. IOVS 2004;45:ARVO E-Abstract 4447)62,78 and temporal peripapillary retina. A possible reason for the higher frequency of fluctuations in the temporal neuroretinal rim is that the BF is lower than on the nasal side.67,81 Boehm et al. suggested that these local differences might be one reason for the preferential damage of the temporal neuroretinal rim in advanced glaucoma.

We used the HRF to follow the ONH capillary BF within the same eye of the same individual. Although using the 10 × 10-pixel measurement window may yield more variable results, nevertheless the method is still valid for the LF. We also used the mixed-effect model for the analysis of data. This model takes into consideration the noise caused by various factors, such as imaging noise. During the HRF image acquisition, we took meticulous care to align images, use the best focus for such unstable locations, as the microvasculature in these areas was not able to regulate the LF appropriately. Fuchsjager-Mayrl et al. suggested that ONH blood supply is regulated by an autoregulation system that acts in normal subjects, in those with hypertensive and preperimetric glucomas, but not in those with advanced glaucoma. Flammer et al. suggested that the hemodynamic alterations may, at least partially, be primarily due to a vascular dysregulation, leading to both low perfusion pressure and insufficient autoregulation. Pillunat et al. found that some disc locations in some individuals do not show autoregulation.

We found that the SBP had a significant positive effect on the mean LF in the uPOAG group over the course of the day. This result is also an indication of an impaired autoregulation at these unstable locations, as the microvasculature in these areas was not able to regulate the LF appropriately. FuchsJager-Mayrl et al. also found an abnormal association between BF and ocular perfusion in patients with POAG.

The topography fluctuated most frequently in the temporal sector for both uPOAG (9/14) and normal subjects (13/14). Overall, a lower BF has been reported in both the temporal neuroretinal rim (Sehi M, et al. IOVS 2004;45:ARVO E-Abstract 4447)62,78 and temporal peripapillary retina. A possible reason for the higher frequency of fluctuations in the temporal neuroretinal rim is that the BF is lower than on the nasal side.67,81 Boehm et al. suggested that these local differences might be one reason for the preferential damage of the temporal neuroretinal rim in advanced glaucoma.

We used the HRF to follow the ONH capillary BF within the same eye of the same individual. Although using the 10 × 10-pixel measurement window may yield more variable results, nevertheless the method is still valid for the LF. We also used the mixed-effect model for the analysis of data. This model takes into consideration the noise caused by various factors, such as imaging noise. During the HRF image acquisition, we took meticulous care to align images, use the best focus for such unstable locations, as the microvasculature in these areas was not able to regulate the LF appropriately. Fuchsjager-Mayrl et al. suggested that ONH blood supply is regulated by an autoregulation system that acts in normal subjects, in those with hypertensive and preperimetric glucomas, but not in those with advanced glaucoma. Flammer et al. suggested that the hemodynamic alterations may, at least partially, be primarily due to a vascular dysregulation, leading to both low perfusion pressure and insufficient autoregulation. Pillunat et al. found that some disc locations in some individuals do not show autoregulation.
Overall, we demonstrated autoregulation of the mean neoretinal rim capillary BF in response to significant diurnal fluctuations of the MOPP. However, we found that in uPOAG there were locations with fluctuating topography that in response to a decrease in MOPP show an increase in mean local flow. We also found that an increase in SBP is associated with an increase in mean LF in uPOAG. The reasons that topography of the ONH fluctuated during the day in both groups is under study in our laboratory.

References

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