Fluctuation in Blood Pressure and Intraocular Pressure in Normal Tension Glaucoma Using Ambulatory Monitoring

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Précis: Ambulatory blood pressure (BP) and intraocular pressure (IOP) monitoring of patients with normal tension glaucoma (NTG) revealed features of vascular dysregulation including hypertension, blunted nocturnal BP dipping, and morning BP surge.

Purpose: The aim was to examine ambulatory fluctuations in IOP and BP in patients with NTG.

Methods: A prospective study of 45 participants with NTG and 10 controls. All participants had a comprehensive ophthalmological examination followed by glaucoma medication washout. Patients using systemic antihypertensives were excluded. IOP and BP were recorded using home monitoring over 48 hours using a self-rebound tonometer and ambulatory blood pressure monitor. BP was recorded every 30 minutes by day and every 60 minutes overnight. IOP was recorded at 09:00, 11:00, 13:00, 16:00, 20:00, and 04:00.

Results: Participants with NTG had a median mean deviation (MD) of −4.66 dB (interquartile range: −7.16 to −2.81 dB) in the worse eye. Among those with glaucoma, 18 of 45 (40%) had normal nocturnal BP dipping, 24 (53%) blunted dipping and 3 (6.7%) exaggerated dipping. Each 10 mm Hg lower minimum sleeping systolic BP was associated with a 0.9 dB (95% confidence interval: 0.1-1.6 dB) worse MD. Sixteen of 45 participants with glaucoma (35.6%) and 1 of 10 controls (10%) were found to have systemic hypertension on ambulatory blood pressure monitoring and 32 of those with glaucoma (71%) had a surge in morning BP, compared with 5 controls (50%). There was no difference in MD between patients with normal, exaggerated and blunted dipping ($P=0.813$).

Conclusions: Though glaucoma has been associated with exaggerated nocturnal BP dipping, we found a higher proportion of patients had systemic hypertension, blunted nocturnal BP dipping, and a morning BP surge, measures also associated with vascular dysregulation.

Key Words: glaucoma, intraocular pressure, blood pressure, home monitoring, self-tonometry

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Glaucoma is a common cause of irreversible visual loss, estimated to affect ~3.5% of the global population aged between 40 and 80 years.[1] The major risk factor is raised intraocular pressure (IOP), however, a sizeable proportion of patients develop glaucoma with IOP in the statistically normal range, suggesting factors other than IOP play a role in glaucoma pathogenesis. The vascular theory of glaucoma proposes that impaired ocular blood flow may contribute to glaucomatous damage, and this may be particularly relevant for patients with low IOP.[2] Reduced ocular perfusion may lead to ischemia of the optic nerve and increased susceptibility to IOP-induced damage, with evidence from epidemiological studies suggesting an association between glaucoma and low ocular perfusion pressure (OPP).[3–5] However, the finding of an association between OPP and glaucoma is not universal[6] and OPP is problematic as a surrogate for optic nerve head perfusion as the method of calculation means its effects cannot be examined independently of IOP and blood pressure (BP).[7] Mean OPP is typically calculated as two-thirds of the mean arterial pressure (MAP) minus IOP, where MAP = diastolic BP + 1/3 (systolic BP − diastolic BP).[8] Despite the debate around OPP, evidence supports a role for vascular dysregulation in glaucoma pathogenesis, and particularly in normal tension glaucoma (NTG).[9,10]

Examination of the relationship between IOP, BP and glaucoma is complicated by normal short-term and long-term fluctuations in both measurements.[11–13] IOP and BP vary over time, and though ambulatory blood pressure monitoring (ABPM) is recommended as a method of assessing BP and diagnosing systemic hypertesion,[14] it is only recently that devices have become available for ambulatory IOP monitoring and these are not widely used.[15] It has been proposed that there is a "U" shaped relationship between BP and glaucoma, where the risk of glaucoma increases at both end of the BP spectrum.[16,17] The typical circadian pattern of BP in normotensive people is highest in the morning and lowest at night.[18] An expected level of nocturnal dip is a 10% to 20% reduction in systolic and diastolic BP, however ~10% have a <10% reduction (blunted dippers) and 20% have a nocturnal dip >20% (exaggerated dippers).[19] Blunted dippers are at increased risk of mortality from cardiovascular events,[13] especially if they also have systemic hypertension;[19] while patients with glaucoma with exaggerated dipping have been reported to be at higher risk of progressive visual field loss, even if IOP is apparently well controlled, suggesting that large nocturnal BP dips may be an additional risk factor in patients with glaucoma.[10,20] High systemic BP has also been linked to an increased risk of glaucoma, in part because of increased episcleral venous pressure leading to reduced aqueous outflow.[21] A recent systematic review suggested that ABPM and careful adjustment and monitoring of antihypertensive

medications could help to protect and preserve visual field in those with glaucoma,[22] however, there is no conclusive evidence that adjusting BP has an effect on ocular perfusion, and measurement of BP is not included as a standard recommended investigation in guidelines for glaucoma diagnosis and monitoring.

The aim of this study was to examine ambulatory diurnal changes in IOP and BP in patients with glaucoma, washed out of topical IOP lowering medications, and to determine if there was a relationship between IOP and BP measurements and severity of glaucoma.

METHODS

A prospective observational study was conducted involving patients with a prior diagnosis of NTG attending a single university hospital glaucoma clinic (Princess Alexandra Eye Pavilion, Edinburgh, UK). All participants had no recorded history of IOP >21 mm Hg in either eye but none had previously had IOP measurements outside the hours of 09:00 to 17:00. A sample of healthy participants were also recruited from advertisements. All participants provided written informed consent and methods were prospectively approved by the South East Scotland Research Ethics Committee. All methods adhered to the principles of the Declaration of Helsinki.

Participants were required to be ≥ 18 years of age and be willing to withhold IOP lowering treatments according to study requirements on the understanding that in the opinion of the investigator they could do so without significant risk. Those who had undergone any form of previous glaucoma surgery or glaucoma laser treatment were excluded; as were potential participants who had undergone previous corneal surgery, including laser refractive surgery, or who had any concomitant corneal disease that may affect IOP readings. Patients using systemic or topical corticosteroids were also excluded, as were those with a known history of systemic hypertension or diabetes.

All participants had a comprehensive ophthalmological examination including slit lamp examination, gonioscopy, dilated fundoscopy, measurement of central corneal thickness using ultrasound pachymetry (Accutome PachPen; Keeler Ltd, Windsor, UK), standard automated perimetry [SAP, 24-2 Swedish Interactive Threshold Algorithm (SITA) Fast, Humphrey Field Analyzer (Carl Zeiss Meditec, Cambridge, UK)] and optical coherence tomography (OCT) measurement of the circumpapillary retinal nerve fiber layer (RNFL) (Spectralis, Heidelberg Engineering, Hemel Hempstead, UK). Glaucoma was defined by the presence of characteristic changes to the optic nerve head or RNFL on dilated fundoscopy or OCT (at least 1 circumpapillary scan RNFL sector classified as outside normal limits), in addition to the presence of a repeatable glaucomatous visual field defect on SAP. All patients with glaucoma had both characteristic changes to the optic nerve head on dilated fundoscopy and an abnormal RNFL on OCT. Previous medical records were reviewed to determine whether there was a history of IOP >21 mm Hg. Following the screening procedure, patients meeting the eligibility criteria were instructed to stop IOP lowering medications for a washout period of up to 42 days depending on the minimum period of 28 days for prostaglandin analogs or beta-blockers, 14 days for alpha-agonists, and 4 days for carbonic anhydrase inhibitors. Medications were only stopped if the investigator felt it was safe to do so. Participants in whom it was not deemed safe were excluded from the study.

Following screening and medication washout, participants attended a baseline visit. At the baseline visit IOP was measured at 09:00 using the Ocular Response Analyzer (ORA G3; Reichert, Buffalo, NY) and Icare HOME rebound tonometer (RT) (Icare, Oy, Finland), operated by a technician. The ORA was used to obtain measurements of Goldmann correlated IOP (IOPg), corneal compensation IOP (IOPcc) and corneal hysteresis (CH). Three measurements were taken from each eye and the measurement with the best waveform score was used for analysis. Only measurements with a waveform score >5 were considered for inclusion. Icare HOME IOP was determined automatically from 6 readings taken during a measurement sequence, with the highest and lowest values automatically discarded and IOP calculated as the mean of the remaining 4 measurements. The order of ORA and Icare HOME testing at the 09:00 baseline visit was randomized. Goldman applanation tonometry was not performed as part of the baseline visit as Goldman applanation tonometry is no longer used for diurnal IOP assessments at our institution. The ORA was selected as it can easily be performed by a technician, is noncontact, produces an objective quality score, and provides IOP measurements compensated for biomechanical properties of the cornea, shown to be highly predictive of future visual field loss.[23,24]

Immediately following the baseline assessment, participants were taught how to measure their own IOP with the Icare HOME using a standardized training protocol.[15] The training session consisted of familiarizing the participant with the Icare HOME tonometer, explaining the user interface, loading a disposable probe, demonstrating the adjustment of the measurement distance from the instrument to the eye, outlining the technique needed to position the tonometer over the central cornea, demonstrating tonometry of right and left eyes and guiding the participant to obtain a measurement from their own eye. These steps were subsequently repeated until the participant could demonstrate consistent and reliable use of the device. Following training, participants were asked to use the Icare HOME to measure their own IOP. They were deemed to have passed training if the IOP measurement from self-tonometry was ≤ 5 mm Hg from the measurement obtained by the technician using the same device. Those who were not able to measure their own IOP were excluded from the study. Participants performing self-tonometry were asked to measure their own IOP at 6 time points (09:00, 11:00, 13:00, 16:00, 20:00, and 04:00) for 2 consecutive days for a total of 12 measurements.

BP was monitored using an ABPM (Model ABPM50; Contec Medical Systems, Hebei, China). Patients wore the cuff on their nondominant arm. The ABPM was programmed to automatically record BP every 30 minutes between the hours of 07:00 and 22:00 and every hour between 22:00 and 07:00. A total of 30 daytime and 9 night-time measurements were taken for each participant during each 24-hour period. All participants were tested for 2 consecutive days aiming for a total of 78 measurements each. During ABPM participants were instructed to continue normal activities and record the time of sleep. The ABPM automatically recorded the date and time of each BP measurement, recording systolic, diastolic, and MAP, in addition to pulse pressure and pulse rate. Patients woke at 04:00 to obtain an Icare HOME measurement. BP was also measured at 04:00 but was regarded as a sleeping BP reading. All IOP measurements were obtained in the sitting position.

Statistical Analysis

Descriptive statistics included mean and SD for normally distributed variables, with normality tested by

inspection of histograms and using Shapiro-Wilk test. ABPM was used to determine whether participants had systemic hypertension, with hypertension defined as an average daytime ambulatory BP ≥ 135/85 mm Hg from the average of at least 14 measurements taken during normal waking hours.[14] ABPM was also used to determine the degree of nocturnal dipping. Nocturnal dipping was defined as normal if there was a 10% to 20% drop in systolic or diastolic BP between wake and sleeping measurements, exaggerated if the drop was > 20%, and blunted if the drops was <10%.[19] SAP MD in the worse eye of participants with glaucoma was compared for those with normal, blunted and exaggerated nocturnal dipping.

Other BP parameters examined included pulse pressure, calculated as the difference between systolic and diastolic BP, which is an indicator of the force generated by the heart each time it contracts. A pulse pressure <25% that of systolic BP is considered abnormally low, whereas a consistently high pulse pressure (eg, > 100 mm Hg) may be because of stiffness of the arteries.[14] The presence of a morning BP surge, identified as a cardiovascular risk factor, was also determined, with morning surge defined as a difference between MAP 2 hours after waking and the mean of the 3 lowest measurements during sleep of > 10 mm Hg.[14]

OPP was estimated for the time points when IOP and BP was recorded simultaneously (04:00, 09:00, 11:00, 13:00, 16:00, and 18:00). OPP was calculated as 2/3×MAP−IOP, where MAP = diastolic BP+1/3 (systolic BP−diastolic BP).[8] Summary measures from home tonometry included mean, peak, and SD IOP. For participants with glaucoma, measurements were compared between worse and better eyes, with worse eye defined as the eye with the worse SAP MD. For healthy participants, 1 eye was chosen at random for inclusion in the analysis. The relationship between BP and IOP parameters and glaucoma severity, measured as SAP MD in the worse eye, was examined using regression analyses. The time of peak and trough OPP was calculated and its relationship to glaucoma severity examined.

All statistical analyses were performed with commercially available software (STATA, version 15.1; StataCorp LP, College Station, TX). The α level (type I error) was set at 0.05.

RESULTS

A total of 52 participants with NTG and 11 healthy controls were included in the study. Forty-five participants with NTG and 10 healthy controls successfully completed the self-tonometry training and were included in subsequent analysis. Demographic and clinical characteristics after medication washout for the 55 participants are shown in Table 1. Participants with glaucoma were on average older than controls, with a median [interquartile (IQ) range] age of 71.0 (63.4 to 76.8) years compared with 54.9 (52.3 to 57.3) years ($P < 0.001$). There was no difference in sex between groups. Median (IQ range) of MD in the worse and better eyes of those with glaucoma was –4.66 (−7.16 to −2.81) dB and −1.62 (−2.76 to −0.68) dB, respectively. Comparisons of worse eyes of those with glaucoma compared with controls, showed lower CH in eyes with glaucoma but no significant difference in IOPg, IOPcc, or mean, peak or SD of IOP from 48 hours of home IOP monitoring. There was also no difference in OPP between worse eyes of participants with glaucoma and controls at any time point (Table 1).

The results of ABPM for participants with glaucoma are summarized in Table 2. A mean (±SD) of 69.1 ± 10.8 BP measurements were taken during waking hours for each participant, versus 15.2 ± 3.0 during sleep. Most sleeping BP parameters were significantly lower than waking hour measures (Table 2), with the exception of average pulse pressure, which was similar between day and night; and minimum pulse pressure, minimum MAP, minimum diastolic BP, and minimum systolic BP, which were all lower during wake compared with sleep (Table 2).

Among participants with glaucoma, 18 of 45 (40%) had normal dipping, 24 (53%) blunted dipping and 3 (6.7%)

TABLE 1. Demographic and Clinical Characteristics of Participants Included in the Study

	Glaucoma (n = 45)			
	Better Eye	**Worse Eye**	**Controls (n = 10)**	***P* (Worse Eye vs. Controls)**
Age (y)	71.0 (63.4-76.8)		54.9 (52.3-57.3)	<0.001*
Sex (female) n (%)	26 (57.8)		5 (50)	0.733†
SAP MD (dB)	−1.62 (−2.76 to −0.68)	−4.66 (−7.16 to −2.81)	−0.17 (−0.60 to 0.28)	<0.001*
CCT (μm)	536 (516-563)	540 (516-562)	578 (546-632)	0.100*
CH (mm Hg)	9.8 (9.1-10.3)	9.6 (9.1-10.4)	11.4 (10.5-12.3)	<0.001*
Intraocular pressure				
Icare IOP (mm Hg) 09:00	13.0 (11.0-17.0)	13.0 (12.0-17.0)	12.5 (11.0-17.5)	0.593*
IOPg (mm Hg) 09:00	15.8 (13.2-18.3)	15.7 (14.0-17.5)	15.9 (14.7-17.8)	0.819*
IOPcc (mm Hg) 09:00	16.6 (14.4-19.7)	16.9 (15.3-18.8)	15.2 (13.6-16.9)	0.104*
Mean home IOP (mm Hg)	13.0 (11.7-15.4)	12.9 (10.6-15.8)	14.3 (11.3-18.9)	0.630*
Peak home IOP (mm Hg)	17.5 (15.0-20.0)	18.0 (15.0-20.0)	19.0 (17.0-22.0)	0.290*
SD home IOP (mm Hg)	2.72 (1.88-3.84)	2.73 (1.85-3.54)	2.42 (2.20-2.97)	0.950*
OPP 09:00 (mm Hg)	59.3 (51.4-69.0)	57.8 (50.6-71.2)	55.5 (46.5-69.8)	0.641
OPP 11:00 (mm Hg)	58.1 (49.9-66.0)	56.6 (49.5-66.0)	55.1 (48.0-66.8)	0.739
OPP 13:00 (mm Hg)	57.8 (48.8-66.8)	57 (49.5-63.0)	56.6 (45.8-68.3)	0.510
OPP 16:00 (mm Hg)	58.1 (47.6-71.6)	60 (48-74.3)	55.5 (33.8-57.8)	0.160
OPP 20:00 (mm Hg)	57 (48-68.2)	57.8 (49.5-69.0)	58.5 (57.0-61.5)	0.674
OPP 04:00 (mm Hg)	59.3 (52.5-68.3)	59.3 (51.0-70.0)	54.8 (51.0-66.8)	0.790

*Wilcoxon rank sum test.
†Fisher exact test.
CCT indicates central corneal thickness; CH, corneal hysteresis; IOP, intraocular pressure; OPP, ocular perfusion pressure; SAP MD, standard automated perimetry mean deviation.

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TABLE 2. Results of 48-Hour Blood Pressure Monitoring in Patients With Glaucoma

	Wake	Sleep	P*
Number of BP measurements	69.1 ± 10.8	15.2 ± 3.0	< 0.001
Average systolic (mm Hg)	125.4 ± 10.2	113.8 ± 14.0	< 0.001
Minimum systolic (mm Hg)	73.6 ± 6.7	92.2 ± 16.5	< 0.001
Maximum systolic (mm Hg)	193 ± 30.6	137.7 ± 21.2	< 0.001
Average diastolic (mm Hg)	125.4 ± 10.2	63.8 ± 7.4	< 0.001
Min diastolic (mm Hg)	33.5 ± 13.4	46.9 ± 10.7	< 0.001
Max diastolic (mm Hg)	138.5 ± 32.1	82.7 ± 18.5	< 0.001
MAP (mm Hg)	89.0 ± 7.2	78.3 ± 9.4	< 0.001
Minimum MAP (mm Hg)	45.1 ± 14.3	58.4 ± 12.6	< 0.001
Maximum MAP (mm Hg)	153.6 ± 27.9	99.4 ± 19.0	< 0.001
Average PP (mm Hg)	51.8 ± 8.2	50.0 ± 11.3	0.072
Minimum PP (mm Hg)	26.0 ± 6.2	36.6 ± 11.4	< 0.001
Maximum PP (mm Hg)	97.4 ± 21.0	65.4 ± 13.7	< 0.001
Average PR (bpm)	74.3 ± 9.5	65.6 ± 9.5	< 0.001

*Two-tailed Student *t*-test.
MAP indicates mean arterial pressure; PP, pulse pressure; PR, pulse rate.

exaggerated dipping. Among controls, 6 of 10 (60%) had normal dipping, 3 (30%) blunted dipping and 1 (10%) exaggerated dipping. Figure 1 shows the distribution of percentage drop in systolic BP in participants with glaucoma. There was no difference the magnitude of average BP dipping observed for glaucoma versus controls, with median percentage reductions of 9.9% (IQ range: 4.3% to 14.2%) and 12.5% (IQ range: 6.4% to 15.8%), respectively ($P = 0.456$). There was no significant difference in worse eye MD between patients with normal, exaggerated and blunted dipping ($P = 0.813$, 1-way analysis of variance with Bonferroni) (Fig. 2).

There was a significant relationship between lower minimum sleeping systolic BP and MD in the worse eye and between higher average daytime pulse pressure and worse SAP MD (Table 3). However, the R^2 values for these relationships were low, indicating that the BP variables accounted for only a small proportion of the variability in MD. There was no significant relationship between IOPg, IOPcc, CH or central corneal thickness or home monitoring IOP values and MD in the worse eye (Table 3).

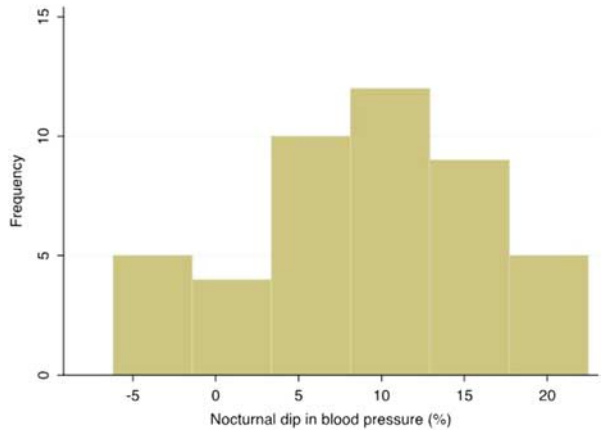

FIGURE 1. Histogram showing the distribution of percentage nocturnal dip in systolic blood pressure in participants with glaucoma. Figure 1 can be viewed in color online at www.glaucomajournal.com.

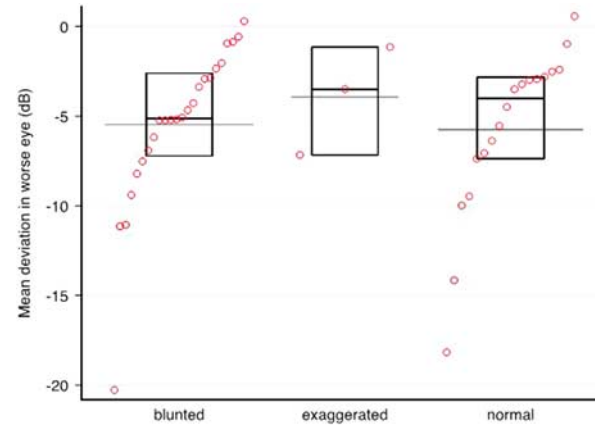

FIGURE 2. Box plot showing the mean deviation in the worse eye for patients with glaucoma with blunted, exaggerated and normal blood pressure dipping. The grey horizontal lines indicate mean values. The limits of the boxes indicate interquartile ranges, with the horizontal lines within the boxes indicating median mean deviation values. Figure 2 can be viewed in color online at www.glaucomajournal.com.

Sixteen of 45 participants with glaucoma (35.6%) and 1 of 10 controls (10%) were found to have systemic hypertension on ABPM. There was no significant difference in MD in the worse eyes of participants with glaucoma in those with systemic hypertension compared with those without (−5.2, IQ range: −9.4 to −2.8 dB and −2.9 IQ range: −5.2 to −1.1 dB, respectively, $P = 0.150$). Thirty-two of 45 participants with glaucoma (71%) had a surge in morning BP, compared with 5 controls (50%). There was no significant difference in MD in the worse eye of participants with glaucoma with a morning BP surge compared with those without (−3.9, IQ range: −7.1 to −2.6 dB and −5.2, IQ range: −8.2 to −2.9 dB, respectively, $P = 0.223$).

Of those with glaucoma, 12 (26.7%) had a peak IOP in the worse eye at 04:00, 6 (13.3%) at 09:00, 8 (17.8%) at 11:00, 10 (22.2%) at 13:00, 6 (13.3%) at 16:00 and 3 (6.7%) at 20:00. Peak IOP in the better eye was at 04:00 in 9 (20%), 09:00 in 8 (17.8%), 11:00 in 8 (17.8%), 13:00 in 5 (11.1%), 16:00 in 10 (22.2%), and at 20:00 in 5 (11.1%). There was no significant relationship between the time of peak IOP and SAP MD in the worse eye ($P = 0.243$, analysis of variance with Bonferroni) (Fig. 3). Figure 4 shows the distribution of OPP in the worse eyes of participants with glaucoma compared with controls. There was no significant relationship between OPP and SAP MD in the worse eye at any time point (Table 3). There was good agreement between baseline (09:00) IOP measurements obtained by the technician using the Icare HOME and IOPg measurements from the ORA, with a mean difference of 2.8mm Hg (95% confidence interval: 2.2-3.3 mm Hg) higher IOP with ORA (IOPg) (see Figure, Supplemental Digital Content 1, http://links.lww.com/IJG/A510, which is a Bland-Altman plot examining agreement between IOPg and IOP from Icare HOME at 09:00 on the baseline visit).

DISCUSSION

The primary objective of this study was to examine IOP and BP fluctuations in glaucoma using ambulatory monitoring in patients washed out of glaucoma medications, with a view to identifying factors associated with glaucoma and worse glaucoma severity. IOP and BP were found to

TABLE 3. Results of Univariable Regression Analysis Examining the Relationship Between IOP and BP Variables and MD in the Worse Eye for Participants With Glaucoma

	Coefficient	*P*	R^2
Age (y)	−0.02 (−0.18 to 0.13)	0.763	0.002
IOPg (mm Hg)	0.17 (−0.12 to 0.45)	0.243	0.032
IOPcc (mm Hg)	0.18 (−0.13 to 0.50)	0.243	0.032
CH (mm Hg)	−0.14 (−1.52 to 1.24)	0.838	0.001
CCT (μm)	0.00 (−0.03 to 0.04)	0.798	0.002
Mean home IOP (mm Hg)	0.22 (−0.11 to 0.55)	0.186	0.048
Peak home IOP (mm Hg)	0.13 (−0.09 to 0.40)	0.229	0.040
SD home IOP (mm Hg)	0.74 (−0.24 to 1.72)	0.132	0.064
Nocturnal BP dip (%)	−0.02 (−0.21 to 0.17)	0.848	0.001
BP surge (%)	0.07 (−0.03 to 0.18)	0.171	0.043
Waking measurements			
Average systolic (mm Hg)	−0.08 (−0.21 to 0.05)	0.202	0.038
Minimum systolic (mm Hg)	−0.02 (−0.09 to 0.05)	0.576	0.007
Maximum systolic (mm Hg)	−0.00 (−0.05 to 0.04)	0.869	0.001
Average diastolic (mm Hg)	0.07 (−0.13 to 0.28)	0.458	0.013
Minimum diastolic (mm Hg)	−0.06 (−0.16 to 0.04)	0.241	0.032
Maximum diastolic (mm Hg)	−0.01 (−0.05 to 0.03)	0.690	0.004
MAP (mm Hg)	−0.01 (−0.20 to 0.18)	0.923	0.000
Minimum MAP (mm Hg)	−0.07 (−0.16 to 0.02)	0.145	0.049
Maximum MAP (mm Hg)	−0.01 (−0.05 to 0.04)	0.815	0.001
Average PP (mm Hg)	−0.18 (−0.34 to −0.03)	0.024	0.113
Minimum PP (mm Hg)	−0.05 (−0.27 to 0.17)	0.636	0.005
Maximum PP (mm Hg)	0.00 (−0.07 to 0.06)	0.878	0.000
Average PR (bpm)	0.01 (−0.13 to 0.15)	0.867	0.000
Sleeping measurements			
Average systolic (mm Hg)	−0.04 (−0.13 to 0.06)	0.435	0.014
Minimum systolic (mm Hg)	0.09 (0.01-0.16)	0.030	0.105
Maximum systolic (mm Hg)	0.01 (−0.06 to 0.07)	0.810	0.001
Average diastolic (mm Hg)	0.09 (−0.09 to 0.27)	0.316	0.023
Minimum diastolic (mm Hg)	−0.10 (−0.22 to 0.03)	0.125	0.054
Maximum diastolic (mmHg)	0.06 (−0.01 to 0.13)	0.093	0.064
MAP (mm Hg)	0.01 (−0.14 to 0.15)	0.927	0.000
Minimum MAP (mm Hg)	−0.09 (−0.19 to 0.02)	0.092	0.065
Maximum MAP (mm Hg)	0.04 (−0.03 to 0.11)	0.293	0.026
Average PP (mm Hg)	−0.10 (−0.21 to 0.02)	0.101	0.061
Minimum PP (mm Hg)	−0.11 (−0.22 to 0.01)	0.068	0.075
Maximum PP (mm Hg)	−0.09 (−0.18 to 0.01)	0.066	0.077
Average PR (bpm)	−0.02 (−0.17 to 0.12)	0.726	0.003
Mean ocular perfusion pressure			
09:00 (mm Hg)	−0.00 (−0.10 to 0.10)	0.982	0.000
11:00 (mm Hg)	−0.01 (−0.11 to 0.10)	0.879	0.001
13:00 (mm Hg)	−0.02 (−0.13 to 0.09)	0.709	0.004
16:00 (mm Hg)	−0.02 (−0.08 to 0.04)	0.505	0.014
20:00 (mm Hg)	0.06 (−0.02 to 0.15)	0.127	0.071
04:00 (mm Hg)	0.00 (−0.09 to 0.10)	0.947	0.000

CCT indicates central corneal thickness; CH, corneal hysteresis; IOP, intraocular pressure; PP, pulse pressure; PR, pulse rate.

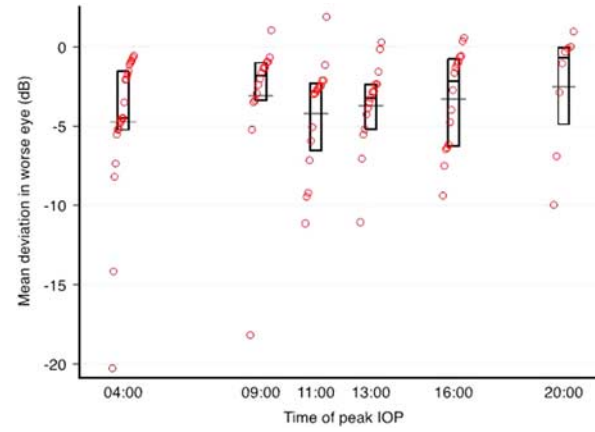

FIGURE 3. Time of peak intraocular pressure (IOP) for patients with glaucoma included in the study and the relationship to disease severity. Figure 3 can be viewed in color online at www.glaucomajournal.com.

fluctuate over a 48-hour period of home monitoring in patients with glaucoma and controls, and home IOP monitoring identified higher peak IOPs than seen at a baseline office hour visit, with a peak IOP of 18.0 mm Hg (IQ range: 15 to 20) on home monitoring in worse eyes of patients with glaucoma compared 13.0 (IQ range: 12.0 to 17.0) at the baseline visit, illustrating a potential value of home IOP monitoring for identification of peak IOP. While it is possible that the higher peak IOP identified during home monitoring was because of measurement error with self-tonometry, all participants had demonstrated the ability to successfully perform self-tonometry and previous studies have shown good agreement between IOP measurements obtained from the home RT and office-based tonometry.[11,15,25]

The magnitude of IOP fluctuation observed during home monitoring was similar between glaucoma patients and controls, and there was no significant relationship between IOP fluctuation and glaucoma severity. Together with the observation of no relationship between peak IOP and MD, this suggests that factors other than IOP may have contributed to glaucomatous

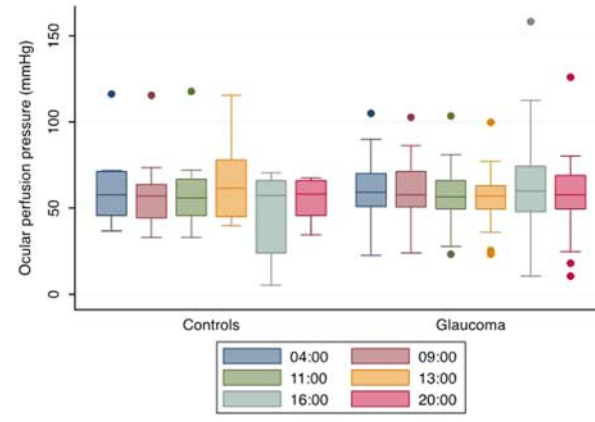

FIGURE 4. Box plot showing mean ocular perfusion pressure at 04:00, 09:00, 11:00, 13:00, 16:00, and 20:00 in participants with glaucoma and controls. Figure 4 can be viewed in color online at www.glaucomajournal.com.

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changes. However, another possible explanation is that the 2-day monitoring period may not have fully characterized historic IOP patterns that had contributed to glaucoma in these individuals. The lack of association may also have been because of the study including only patients with a baseline diagnosis of NTG, and only including patients with mild to moderate glaucoma because of the need to conduct a medication washout.

Home BP monitoring also showed significant fluctuation, and there were significant differences in BP between wake and sleep, with lower average systolic and diastolic BP, lower average MAP and lower average PR (Table 2). Maximum PP, maximum MAP, maximum systolic BP, and maximum diastolic BP were also all lower during sleep. There were consequent changes in OPP observed over the 48-hour period, though median OPPs were similar across time points (Table 1). The analysis comparing BP metrics and MD in the worse eye, found minimum systolic BP during sleeping to have the strongest association with MD. Each 10mm Hg lower systolic BP was associated with a 0.9 dB (95% confidence interval: 0.1-1.6 dB) reduction in MD in the worse eye, supporting previous studies showing an association between systemic hypotension and glaucoma.[10,16] It is, however, possible that this finding was a type II error, as we included a large number of comparisons, and failed to find an association between the degree of nocturnal BP dipping and glaucoma, or the other BP metrics and SAP MD. It was surprising that only 6.7% of patients with NTG had exaggerated nocturnal BP dipping, which was a similar proportion as controls. Blunted dipping was more common, observed in over 50% of patients with NTG compared with 30% of controls. Despite previous studies suggesting exaggerated dipping to be a risk factor for glaucoma progression,[10] albeit using cross-sectional analysis, we found no relationship between nocturnal BP dipping and glaucoma severity (Fig. 2). Unfortunately, we were not able to conduct an analysis of IOP differences between wake and sleep as only 1 IOP measurement was taken during the sleeping period, at 4 AM. An advantage of ABPM compared with the RT is that the ABPM obtains measures automatically and does not require the patient to wake to obtain a measurement, making multiple night-time measurements more feasible.

Several previous studies have found an association between ABPM measurements and glaucoma.[26–28] Yilmaz et al[27] found that lower daytime systolic BP, night-time systolic BP and whole day systolic BP were risk factors for developing glaucoma. They suggested that ABPM might be indicated in patients who demonstrate glaucoma progression. Jin et al[28] found that patients with early NTG who had a paracentral scotoma on visual field testing had a larger nocturnal dip in BP and suggested that ABPM should be performed in this subset of patients. ABPM may also highlight glaucoma patients who are extreme dippers so that they can be managed appropriately, for example, by changing the timing of antihypertensive drugs to minimize the risk of optic nerve ischemia at night.[16]

Despite these previous observations, we found a lack of association between ABPM measurements and glaucoma severity. Though this might suggest ABPM is of limited value in glaucoma management, the study was limited by a small sample size and a cross-sectional design. In addition, we did not attempt to target patients for inclusion who may have had higher chances of BP abnormalities in whom ABPM may be more likely to detect dipping. For example, had we recruited only patients with demonstratable visual field progression, or those with symptoms of orthostatic hypotension, we may have found a higher incidence of nocturnal BP dipping, but because of the need for a medication washout, we excluded patients with advanced glaucoma and those with recent progressive changes. Collignon et al[26] suggested that nocturnal dipping should be thought of as a predictive risk factor for progression in glaucoma, and it may be that the patients with exaggerated BP dipping in this study will be at higher risk of future progression. In subsequent work it would be useful to examine a larger number of exaggerated dippers and follow them over time, as this would help to determine whether exaggerated nocturnal dipping is a risk factor for progression of glaucoma. The small proportion of patients with exaggerated BP dipping observed in our study, suggests however, that a large number of patients would need to be screened to conduct such an investigation.

Despite the small number of participants with nocturnal dipping, we found ABPM to detect a high number of potentially important abnormalities, with the most striking finding the large proportion of participants found to have systemic hypertension. According to the UK National Institute for Health and Care Excellence (NICE), hypertension can be diagnosed based on an average daytime ambulatory BP $\geq$ 135/85 mm Hg from the average of at least 14 measurements taken during normal waking hours.[14] We found 16 of 45 participants with glaucoma (35.6%) and 1 of 10 controls (10%) fulfilled this criterion. Though hypertension is a known risk factor for glaucoma and is common in the elderly population, the high number of undiagnosed hypertensives was surprising.[29] ABPM also showed that 32 (71.1%) of the patients with glaucoma had a surge in BP in the morning. Morning surge is associated with a higher risk of cardiovascular and cerebrovascular disease.[30,31] We also found that there was a significant drop in BP during sleep, which is a well-known phenomenon, however, the average percentage reduction in nocturnal BP for patients with glaucoma and healthy controls was not significantly different at 9.9% and 12.5%, respectively ($P = 0.456$). We had expected a large proportion of patients with NTG to have exaggerated nocturnal dipping, however, this was observed in only 3 participants (6.7%), while 24 (53.3%) showed blunted nocturnal dipping. Similar, to morning surge, blunted nocturnal dipping or nondipping is associated with silent cerebrovascular damage[32] and increased risk of cardiovascular events.[32,33] These findings could indicate that patients with NTG have generalized vascular dysregulation that puts them at risk not only of glaucoma, but also systemic cardiovascular and cerebrovascular disease. The lack of an association between glaucoma and exaggerated nocturnal BP dipping was surprising but may have been because of the high proportion of patients with undiagnosed systemic hypertension. In a cross-sectional study of 314 patients with glaucoma, Pillunat et al[34] found that patients with daytime systemic hypertension, who also exhibited exaggerated nocturnal BP dipping, had less severe visual field loss than those with daytime systemic normotension who also had exaggerated nocturnal dipping. Exaggerated nocturnal dipping may therefore have a greater association with glaucoma in individuals with normal daytime BP.

It is important to emphasize that none of the participants recruited to this study were taking systemic antihypertensive medications. It would be interesting to see if those taking antihypertensives were more likely to have an

exaggerated nocturnal dip. Hayreh et al[35] found that NTG patients taking antihypertensive medications had a significantly larger nocturnal dip, which was not found to be the case in unmedicated patients with and without hypertension. As patients taking antihypertensives were excluded, this might explain why there were fewer than expected exaggerated nocturnal dippers. We also found no significant difference in OPP between patients with NTG and controls, and OPP was not significantly associated with MD. This finding contradicts Choi et al[36] who found that circadian mean OPP fluctuation was a significant predictor of advanced glaucomatous damage and Raman et al,[37] who found that lower diastolic OPP was a risk factor for progression in patients with NTG. Interestingly, in the present study, there was no significant difference in baseline IOP, IOPg and IOPcc, or in mean IOP, peak IOP and SD of IOP during home monitoring between participants with glaucoma and controls. This is most likely because we only included patients with NTG, though it may suggest a non-IOP related mechanism for glaucomatous optic neuropathy in this particular cohort.

Limitations of the study include the small number of participants in the control group and the significantly younger age of controls compared with those with glaucoma. Systemic hypertension is more common in older subjects, which might explain the higher than expected levels of hypertension in the NTG group, which had an average age of 71 years. This likely reduces the generalizability of the results to younger patients with NTG, who are likely to have lower levels of atherosclerosis and hypertension. Nevertheless, the finding of a high prevalence of undiagnosed hypertension in the NTG group is of potential importance, providing further evidence of possible vascular dysregulation in patients with NTG. Further limitations included the use of a theoretical formula for calculation of OPP, which may not accurately reflect true ocular perfusion; and the lack of examination of the potential impact of patient positioning of BP and IOP, which is known to be affect measurements of both parameters.[38] Though devices are available for measurement of IOP in the supine position, including the iCare PRO RT,[39] none are designed for self-tonometry. We opted to use the Icare HOME as it is design for self-tonometry but acknowledge that the IOP readings obtained at night may not reflect IOP in the supine position.[40] A further limitation is that ambulatory measurements were only obtained over a 2-day period and it is possible that a longer duration of monitoring may have produced different results.

In conclusion, the results of this study do not provide sufficient evidence to support universal routine home monitoring of BP using ABPM for glaucoma patients. However, there may be a role for ABPM in selected patients, for example, those with progressive visual field loss despite low IOP, those with symptoms of hypotension, and in progressing patients using systemic antihypertensives. Though glaucoma has been associated with hypotension and exaggerated nocturnal BP dipping, we found a higher proportion of patients had systemic hypertension, blunted nocturnal BP dipping, and a morning BP surge, suggesting that some patients with NTG may have associated generalized vascular dysregulation, potentially increasing the risk of cardiovascular and cerebrovascular disease.

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