Glaucoma

Twenty-four Hour (Nyctohemeral) Rhythm of Intraocular Pressure and Ocular Perfusion Pressure in Normal-Tension Glaucoma

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Purpose. To characterize the nyctohemeral rhythm of intraocular pressure (IOP) and ocular perfusion pressure (OPP) in patients with newly diagnosed, untreated normal tension glaucoma (NTG).

Methods. Twenty-seven patients with suspected NTG were prospectively included and underwent 24-hour monitoring of IOP and blood pressure (BP), polysomnography, and nailfold capillaropathy. The nyctohemeral rhythms of IOP, BP, and OPP were modeled with a nonlinear least-squares, dual-harmonic regression procedure, studying the mean value, the acrophase, the nadir and the amplitude of each rhythm. Nonparametric tests were used to study the relationship between the rhythm of IOP and vascular, sleep, and visual field parameters.

Results. Five patients were excluded from the analysis after the 24-hour curve of IOP, (IOP > 21 mm Hg during nighttime [n = 1] or daytime [n = 4]). Twenty-two (81%) patients received a diagnosis of NTG (IOP < 22 mm Hg over 24 hours). They exhibited a diurnal acrophase (54.5%), or a nocturnal acrophase (36.4%) of IOP. The remaining patients (9.1%) with NTG had no nyctohemeral rhythm. A significantly higher proportion of patients with capillaropathy and a higher nyctohemeral fluctuation of IOP characterized the IOP group with diurnal acrophase. A rhythm of OPP was found in all patients, (diurnal [58%] or nocturnal [42%]) acrophase) equally distributed between the two groups of IOP. Amplitude of OPP was not significantly associated with the severity or progression of glaucoma.

Conclusions. A nyctohemeral rhythm of IOP exists in most of the patients with NTG, either with a nocturnal acrophase or a diurnal acrophase. The rhythm of OPP did not correlate with the IOP rhythm. (*Invest Ophthalmol Vis Sci.* 2010;51: 882–889) DOI:10.1167/iovs.09-3668

Normal tension glaucoma (NTG) is a progressive optic neuropathy characterized by typical optic nerve head cupping, visual field defects and the absence of increased intraocular pressure (IOP). In real life, this definition is mainly based on diurnal measurements of IOP, with values within the normal range of less than 22 mm Hg.[1] However, nyctohemeral (24-hour) measurements of IOP are necessary to detect patients with elevated nocturnal IOP. The day–night variations of IOP have been analyzed in healthy subjects[2-4] and in patients with primary open-angle glaucoma,[5,6] but the existence of nyctohemeral variations of IOP in NTG is still debated. Understanding IOP-independent mechanisms in NTG is also crucial since vascular factors including nocturnal blood pressure (BP) reduction,[7,8] migraine, and vasospasms[9,10] were identified as possible pathophysiological factors. Recent reports have emphasized the potential role of ocular blood flow dysregulation in NTG, such as a nocturnal reduction of ocular perfusion pressure (OPP).[11] These factors were necessary to determine and characterize the 24-hour profile of IOP and OPP in patients with NTG.

MATERIALS AND METHODS

This prospective cohort included 27 Caucasian patients (6 men and 21 women) with suspected NTG, from April 2004 to January 2006. All patients agreed on the investigation and gave their informed consent after explanation of the nature and possible consequences of the study, in accordance to the tenets of the Declaration of Helsinki. The potential benefit of participating in this study was also explained (diagnosis of NTG and obstructive sleep apnea syndrome; [OSAS], and characterization of the IOP profile for a better local hypotensive therapy).[12] The study protocol was approved by the local Institutional Review Board (Comité de Protection des Personnes, Sud-Est V).

Patients were eligible if they had a glaucomatous-appearing optic nerve head in addition to corresponding visual field loss and maximum diurnal IOP < 22 mm Hg reported on a previous diurnal IOP curve (hourly measurements from 0900 to 1800 hours, using Goldmann tonometry). The eligible eye was the one with a more advanced glaucomatous field defect based on the mean defect (MD) of the Humphrey visual field. If both eyes exhibited similar damage (five patients), one eye was chosen at random and used for statistical analysis.

Exclusionary criteria were as follows: presence of intracranial lesion (confirmed by computer tomography or/and magnetic resonance imaging), a history of massive hemorrhage or hemodynamic shock, or presence of history of any other ocular disease that could result in a visual field defect. Patients treated with antihypertensive drugs were not excluded except for those treated with systemic β-blockers, which are known to have the potential to affect IOP. Eight patients were treated for systemic hypertension with diuretics (n = 2), angiotensin II

inhibitors ($n = 2$), central antihypertensive drugs ($n = 3$), and/or calcium blockers ($n = 1$).

For the experiment, the subjects were housed in a sleep laboratory for 24 hours that included a controlled environment: sitting position from 0800 to 2100 hours, supine position from 2100 to 0800 hours, a light–dark cycle, constant temperature, and controlled fluid intakes and meals. All patients were asked to adhere to a regular 24-hour sleep–wake cycle (timing and duration of sleep) for 4 weeks before the 24-hour study.

Visual Field Examination

Visual field examinations were performed with retinal perimetry (the 24-2 Swedish Interactive Threshold Algorithm standard program on the Humphrey Field Analyzer; Carl Zeiss Meditec Inc., Dublin, CA). Eyes with glaucomatous visual field defects were defined as those that met all the criteria of the European Glaucoma Society.[13] All patients had a reliable visual field test, defined as a false-positive error of less than 15%, a false-negative error of less than 15%, and a fixation loss less than 20%. Visual field data for analysis were mean defect (MD), PSD, and the Advanced Glaucoma Intervention Study (AGIS) score.[14] The progression of the disease was also evaluated with the AGIS criteria[15] (a worsening of the visual field confirmed by a single test after 6 months was defined as a variation in MD of 2 dB). The visual fields (Fastpac 24/2, Humphrey; Carl Zeiss Meditec) were also graded for severity according to the classification of Hodapp and Anderson.[16]

Measurements of IOP and Corneal Thickness

Central corneal thickness was measured by ultrasonic pachymetry (Pocket II; Quantel Medical, Clermont-Ferrand, France).

After a washout period of their topical glaucoma medications 1 month before the experiment, IOP was evaluated over 24 hours on the eligible eye every hour between 0800 the first day and 0800 hours the day after. IOP was measured in subjects in a sitting position between 0800 and 2000 hours and in a supine position from 2100 to 0700 hours, with an electronic tonometer (Tono-Pen; Oculab, Glendale, CA)[17] after the instillation of a contact anesthetic (Oxybuprocaine; Novartis Pharma, Rueil-Malmaison, France). The value was the mean result of three to six consecutive measurements, until the intermeasure variability was less than 5%. The correlation between IOP measurements using the tonometer (Tono-Pen; Oculab) and the Goldmann tonometer was excellent, as reported in a previous experiment in the same laboratory ($n = 100$ measurements, 14 healthy patients, $r = 0.98$, $P < 0.001$, unpublished data) and a study by Kao et al.[18] ($r = 0.84$ and 0.87 in right and left eyes). The difference between both techniques was lower than 1 mm Hg in 88% of the cases. At night, the subjects were awakened hourly for IOP measurements, remaining in bed. The duration of IOP measurements, including the anesthetic instillation, was 59.3 ± 0.7 seconds during the night and the total awakening (determined by electroencephalogram recording) resulting from the IOP measurement averaged 123.1 ± 1.7 seconds.

Measurement of Hemodynamic Parameters

BP was evaluated over 24 hours with measurements taken every 15 minutes during the day and every 30 minutes during the night with an ambulatory brachial sphygmomanometer (Diasys Integra; Novacor SA, Rueil-Malmaison, France). Mean arterial pressure (MAP) and OPP[19] were calculated as follows: (1) MAP = DBP + ⅓(SBP − DBP), (2) $OPP_{sitting} = (95/140 \times MAP) - IOP$, and (3) $OPP_{supine} = (115/130 \times MAP) - IOP$, where SBP is systolic blood pressure and DBP is diastolic blood pressure.

MAP was averaged per hour. MAP fluctuations were defined as the mean of the difference between the highest and the lowest MAP during daytime or nighttime. Nocturnal BP reduction was calculated as $100 \times (1 - sleep SBP/awake SBP)$. We classified the patients by the decline in nocturnal BP as follows: extreme dippers if the nocturnal BP fall was ≥20%, physiologic dippers if the fall was ≥10% but <20%, nondippers

if it was ≥0% but <10%, and reverse dippers if the BP increases during sleep.[12,20,21]

Capillaropathy was suspected on the basis of a history of migrainous headache or Raynaud's phenomenon and confirmed by a nailfold capillaroscopy.

Polysomnography

An overnight polysomnography was performed during spontaneous breathing to characterize abnormal respiratory events during sleep according to standard criteria,[22] as previously described.[23] Polysomnography was performed in the last consecutive 16 patients and was unavailable in the first 6 patients. A hypopnea was measured when a 50% reduction in nasal pressure signal (continuous recording of inspiratory and expiratory pressure) was associated with a desaturation of 4% (4% drop of oxygen blood pressure from baseline) and/or a microarousal (abrupt shift in electroencephalogram frequency).[22,24] Apneas were defined as a 10-second pause in respiration during sleep. An apnea–hypopnea index (AHI) of 15 events per hour was the criterion that defined OSAS.[22]

Modeling of the Nyctohemeral (24-hour) Rhythms of IOP, BP, and OPP

A nonlinear least-squares, dual-harmonic regression analysis was used to model the 24-hour rhythms of IOP, BP, and OPP.[25] To model each rhythm, two sinusoids were fit: the first (the fundamental), constrained to 24 hours to take into account that rhythms were measured during a 24-hour sleep–wake cycle, having a large amplitude, and the second (the first harmonic), having a relatively low amplitude but altering the general shape. Unbiased estimates and confidence limits of amplitude ((acrophase-nadir)/2), mesor (mean), and acrophase (time of the highest value) were obtained from the waveform of each rhythm.

Statistical Analysis

Descriptive statistics were presented as number and percentage for categorical variables and mean ± SD for continuous variables. Figures show the mean ± SEM for better readability. A χ^2 test was used to detect the difference between groups for categorical variables. For continuous variables, the nonparametric Mann-Whitney test was performed to detect the difference among groups (SPSS software (12.0); SPSS, Chicago, IL). Differences reaching $P < 0.05$ were considered statistically significant.

RESULTS

Twenty-two (81.4%) patients were included in the analysis; 5 of the 27 patients initially screened were excluded from the analysis due to high IOP (IOP > 21 mm Hg during nighttime in 1 and during daytime in 4) during the 24-hour measurement. Anthropometric, sleep, and BP data of the patients are summarized in Table 1. In the general population of patients with NTG, there was a predominance of women, a systemic hypertension in 64% of the cases (defined as average 24-hour ambulatory systolic BP ≥ 130 mm Hg or diastolic BP ≥ 80 mm Hg) and a capillaropathy in 40.9%.

The nocturnal BP variation was classified as physiological dipper in 18.2% of the cases (4/22), overdipper in 4.5% (1/22), nondipper in 54.6% (12/22), and reverse dipper in 22.7% (5/22). Among the 16 last patients systematically investigated for polysomnography, 81.2% had a diagnosis of OSAS.

After modeling of the 24-hour curves of IOP, the patients were classified as either having a diurnal IOP rhythm (i.e., with a diurnal acrophase, $n = 12$, 54.5% of the cases, Figs. 1, 2), an absence of IOP rhythm ($n = 2$, 9.1%, Fig. 1), or a nocturnal IOP rhythm (i.e., with a nocturnal acrophase, $n = 8$, 36.4%; Figs. 1, 3). Since the group without any rhythm of IOP included only two patients, statistical comparisons were performed between

TABLE 1. Patients Demographics, Sleep, and Vascular Parameters

	All Patients (n = 22)	Patients with Diurnal Acrophase of IOP (n = 12)	Patients with Nocturnal Acrophase of IOP (n = 8)	χ^2 Test or Mann-Whitney Test (P)
General data				
Age, y	68.41 ± 11.55	70.33 ± 11.80	63.00 ± 10.58	0.1
Sex, M/F	6/16	2/10	4/4	0.1
Body mass index	25.10 ± 5.26	24.07 ± 3.66	23.67 ± 4.51	0.9
Arterial hypertension, %	64	67	50	0.3
Polysomnographic data (n = 16)				
Obstructive sleep apnea, %	81.25	66.72	80.00	0.54
Apnea and hypopnea index, events/hour of sleep	28.56 ± 15.64	21.80 ± 10.74	29.40 ± 14.66	0.2
Total sleep time (min)	316.18 ± 76.92	313.60 ± 73.01	319.86 ± 88.05	0.8
Stages 3–4, % of total sleep time	13.13 ± 10.75	10.37 ± 7.52	17.44 ± 14.04	0.3
Vascular factors				
Capillaropathy, %	**40.9**	**67**	**13**	**0.028**
Mean MAP, mm Hg	94.73 ± 11.73	95.32 ± 12.36	95.40 ± 11.43	0.92
Night MAP, mm Hg	90.65 ± 13.23	89.50 ± 13.22	93.07 ± 14.50	0.77
Day MAP, mm Hg	96.47 ± 12.39	97.50 ± 13.83	97.11 ± 10.12	0.68
MAP rhythm, %				0.5
Diurnal	77.3	75	87.5	
Nocturnal	22.7	25	12.5	
MAP amplitude	8.58 ± 2.91	9.28 ± 3.27	7.76 ± 2.55	0.5
MAP fluctuation	8.58 ± 3.51	8.92 ± 2.84	7.68 ± 4.35	0.1
Diurnal	8.22 ± 4.88	8.98 ± 6.36	7.33 ± 2.19	0.7
Nocturnal				
Mean percentage decrease in nocturnal BP				
Systolic BP, %	27.02 ± 10.99	29.94 ± 11.14	23.69 ± 10.96	0.8
Diastolic BP, %	34.05 ± 13.18	35.14 ± 9.01	33.58 ± 18.54	0.4
Mean OPP, mm Hg	56.11 ± 9.29	56.30 ± 10.25	57.20 ± 8.33	0.6
Night OPP, mm Hg	55.58 ± 10.05	55.10 ± 9.43	57.13 ± 11.59	0.6
Day OPP, mm Hg	56.47 ± 10	57.08 ± 11.59	57.38 ± 7.80	0.57
OPP rhythm, %				
Diurnal	58	60	62.5	0.6
Nocturnal	42	40	37.5	
Amplitude OPP	6.56 ± 2.81	6.07 ± 2.88	7.29 ± 2.92	0.4
Physiological dipper, %				
Yes	18.2	25	12.5	0.4
No*	81.8	75	87.5	

Data are expressed as the mean ± SD; all data were recorded over a 24-hour period. Statistics have been performed to compare the diurnal and the nocturnal groups. The statistically significant parameter is in bold.

* Included nondippers, reverse dippers, and overdippers.

the groups of diurnal and nocturnal acrophase. OPP was classified as either diurnal (58% of the cases) or nocturnal (42%) according to the time of the acrophase.

The distribution of sex and systemic hypertension was not significantly different among groups of nocturnal and diurnal IOP rhythm (Table 1). Age, body mass index (Table 1), mean 24-hour IOP, and mean diurnal IOP (Table 2) were statistically similar among the groups. The nocturnal decrease of BP, estimated by the mean percentage decrease in systolic or diastolic BP, and MAP fluctuations were similar in both groups of IOP rhythm (Table 1). None of the patients treated for systemic hypertension were physiological dippers, whereas 28.6% of the patients without systemic hypertension were physiological dippers (P = 0.04).

No correlation was found between amplitudes of IOP and those of OPP (P = 0.57), and no association was found between the type of rhythm of IOP and OPP (P = 0.9; i.e., in each group of IOP rhythm). We found approximately 60% of cases to have diurnal rhythm of OPP.

The diurnal group of IOP differed from the nocturnal group (Table 1) by higher amplitude of IOP (P = 0.025) during the 24-hour course and a higher frequency of capillaropathy (P = 0.028).

The proportion of patients with OSAS was similar in both groups of IOP rhythm. The patients had capillaropathy (5/22, 22.3%), OSAS (9/16, 56.2%), or both (4/22, 18.2%). Only four patients (4/22, 18.2%) had no capillaropathy and no symptoms of OSAS (they were not investigated with polysomnography). Among the ocular parameters (Table 2), no significant difference was noted between both groups of IOP rhythm in visual acuity, corneal thickness, or visual field parameters. Mean defects, Hodapp classification, and AGIS score did not correlate significantly to amplitudes of IOP, OPP, or MAP.

The rhythm of OPP was strongly associated with that of BP (P = 0.005). Amplitude of OPP was not significantly associated with the severity of glaucoma at inclusion (Hodapp classification, P > 0.5) or to the progression of glaucoma (AGIS score, P = 0.3).

DISCUSSION

This study reports the first characterization and modeling of the nyctohemeral rhythm of IOP of patients with NTG. Nearly 90% of the patients with NTG exhibited either a diurnal or a nocturnal acrophase of their IOP rhythm.

FIGURE 1. Average nyctohemeral rhythms of IOP in three groups of patients with NTG. Each curve of IOP was mathematically modeled with a nonlinear least-squares, dual-harmonic regression procedure and classified as nocturnal acrophase (rhythm with a nocturnal peak, $n = 8$), diurnal acrophase (rhythm with a diurnal peak, $n = 12$), or an absence of rhythm (no rhythm, $n = 2$). Graphs represent the average variations of IOP $\pm$ SEM during a 24-hour period in each group of patients.
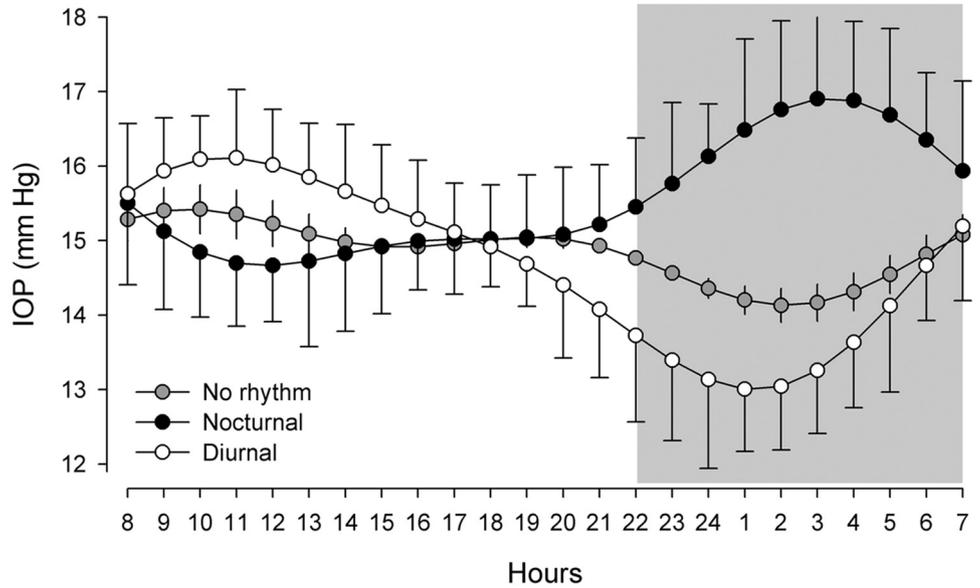
The methodology of the study was unique, with IOP measurements every hour in a physiological posture (sitting during daytime and supine during night-time)[2,5] and in controlled environmental conditions. IOP, BP, and OPP data were then mathematically modeled and classified according to the waveform and the acrophase of their nyctohemeral rhythm. Given the complexity of hourly measurements of IOP, previous studies in patients with NTG included data of IOP obtained only every 2 to 3 hours over 24 hours.[11,26–28] Hourly measurements made modeling of the rhythms significantly more precise and meaningful.[2,5] The nonlinear least-squares, dual-harmonic regression procedure[25] that we used in this study has the advantage of being applicable to all sorts of rhythm and not exclusively for monophasic rhythms and does not assume a priori that a rhythm is sinusoidal, in contrast with the cosinor technique, least-squares regression with a single cosine. Furthermore, it is methodologically incorrect to pool data of IOP from different groups of patients with different rhythms, because mean profiles would not reflect true individual variations across the day, but would represent the average of low values of some eyes with high values measured for other eyes. Hence, mean calculations are correct only in patients who have been previously classified in homogeneous groups of IOP rhythms. Therefore, interstudy comparisons are difficult since the study design is often different (type of tonometer, frequency of measurements, calculations and modeling of nyctohemeral variations).

Data from this study showed that two major IOP rhythms exist in NTG, either with diurnal (54%) or nocturnal (36%) acrophase. Previous studies described the diurnal variations of IOP,[29] and only three studies reported 24-hour variations of IOP in this population.[27,28,30] The first series,[27] from Japan, included 73 patients with NTG with the recording of IOP every 2 hours. Maximal IOP was mainly observed at 0400, 1000, and between 1600 and 1800 hours. The second study[28] including 69 Japanese patients reported IOP measurements every 3 hours with maximum IOP at different times (0300, 1200, 1800, and 2400 hours). The third study[30] was conducted in 30 Caucasians with IOP measurements every 4 hours and maximum IOP values mainly observed at 0400 hours. Although many limitations of these studies exist, including measurements of IOP in the sitting position across the 24-hour period, the number of measurements (6–12 values/24 hours), the absence of modeling of the IOP rhythm, and the noncontrolled

FIGURE 2. Nyctohemeral variations of IOP and fitting by the nonlinear least-squares, dual-harmonic regression procedure in eight patients with NTG with nocturnal acrophase. Data represent the average variation of IOP $\pm$ SEM during a 24-hour period.
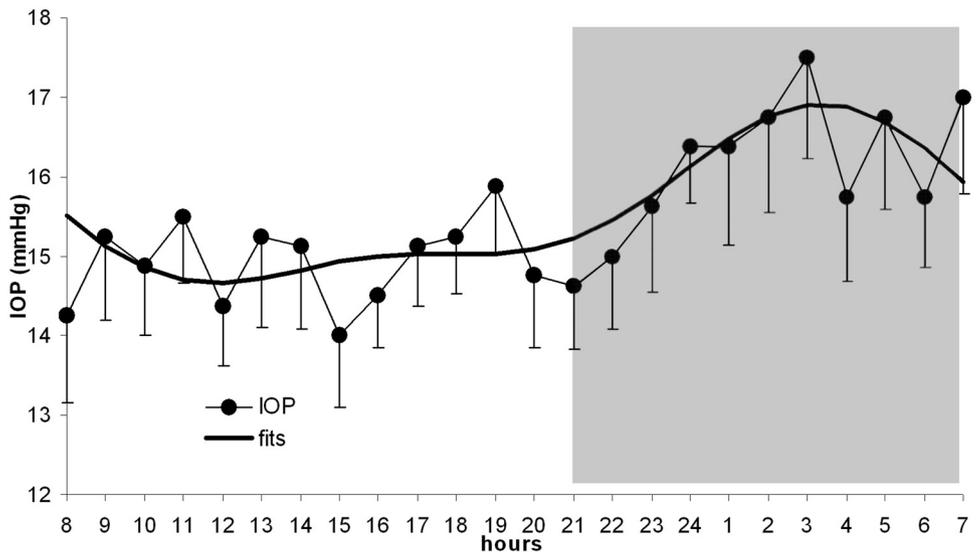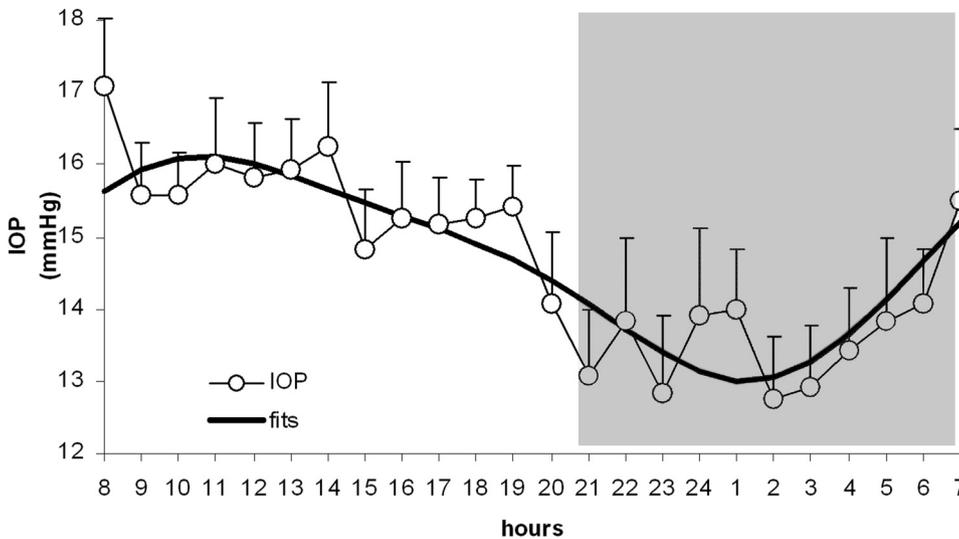
FIGURE 3. Nyctohemeral variations of IOP and fitting by the nonlinear least-squares, dual-harmonic regression procedure in 12 patients with NTG with diurnal acrophase. Data represent the average ± SEM variations of IOP during a 24-hour period.

environmental conditions, their results are consistent with the existence of either a diurnal or a nocturnal acrophase in patients with NTG, as shown in our study.

Fluctuations are usually defined as the difference between the highest and the lowest values recorded over the 24-hour period, which makes this measure very sensitive to artifacts or acute changes evoked by the environment. In our study, amplitude of IOP was calculated after modeling of the IOP rhythm. In the general population of patients with NTG in our series, the mean fluctuations (4.08 mm Hg) were similar to that reported in diurnal or nyctohemeral studies, between 4.0 and 5.5 mm Hg in patients with untreated NTG.[26,27] The highest amplitude of IOP was associated with a diurnal IOP rhythm. The clinical consequences of this result are not known, and no correlation between IOP and OPP amplitude or the severity or progression of glaucoma[31–33] was found in our series.

Highlighted by recent studies in the field of glaucoma (for reviews, see Refs. 12, 34), 24-hour IOP and OPP monitoring are essential in NTG for different reasons: (1) exclusion of false diagnosis of NTG among patients with suspected glaucoma, (2) choice of the local hypotensive treatment with the better chronotherapeutic profile,[12,34] (3) detection of nocturnal BP

reduction, and (4) a better understanding of the mechanisms of this disease.

Exclusion of false diagnosis of NTG with IOP values above 21 mm Hg during daytime or nighttime is necessary in clinical and therapeutic studies,[12] and represent between 11% and 20% of the suspected cases of NTG (including our series).[27]

The pathophysiological signification of these IOP rhythms is unknown. In the literature, a few studies have explored physiological changes in patients with NTG. For instance, episcleral venous pressure is higher and differs in patients with POAG or NTG compared with healthy humans.[35] On the other hand, no significant difference of outflow has been reported between normal subjects and patients with NTG.[36] Predominance of women,[37] arterial hypertension,[37,38] and a low corneal thickness[39] were reported in this study with a frequency consistent with other series in the literature. Of interest in our study, 58% of patients with NTG exhibited a diurnal acrophase and 42% a nocturnal acrophase of OPP. These results in NTG differ from those in normal subjects with peak OPP noted in the nocturnal period.[6] The nyctohemeral parameters of OPP did not correlate with the type of IOP rhythm, which could suggest that lowering IOP in a certain manner will not change OPP in a

TABLE 2. Ocular Parameters in the Different Groups of IOP Rhythm

	All Patients (*n* = 22)	Patients with Diurnal Acrophase of IOP (*n* = 12)	Patients with Nocturnal Acrophase of IOP (*n* = 8)	χ^2 Test or Mann-Whitney Test (*P*)
IOP data, mm Hg				
Mesor	14.95 ± 1.96	14.67 ± 2.06	15.47 ± 2.8	0.3
Amplitude	**2.04 ± 1.31**	**2.62 ± 1.46**	**0.65 ± 0.06**	**0.025**
Diurnal mean	15.4 ± 2	15.58 ± 2.15	15.13 ± 2.1	0.5
Nocturnal mean	**14.9 ± 2.8**	**13.67 ± 2.46**	**16.63 ± 2.2**	**0.016**
Clinical data				
Visual acuity, logMAR	0.22 ± 0,3	0.24 ± 0.31	0.21 ± 0.34	0.7
Pachymetry, μm	523 ± 29.77	518 ± 36.4	530 ± 21.4	0.8
Cup/Disc ratio	0.68 ± 0.19	0.69 ± 0.15	0.67 ± 0.2	0.7
MD, dB	−10.78 ± 6.9	−8.98 ± 5.4	−13.34 ± 8.7	0.3
Hodapp classification, %				
Early defect	27.2	33.3	25	0.8
Moderate defect	45	41.6	37.5	
Severe defect	27.3	25	37.5	
AGIS score	6.59 ± 5.22	5.92 ± 5.63	8.3 ± 5.1	0.2
Evolution AGIS, %	27.3	33,30	25	0.7

Bold data are statistically significant.

similar profile. This result is not surprising, due to the formula of OPP,[19] relating a high importance of BP (multiplied by a factor of 0.67 in sitting position or 0.88 supine) compared with IOP values. Hence OPP rhythm is essentially linked to the BP rhythm, a conclusion is consistent with that found by Choi et al.[26] (marked circadian of OPP fluctuations were associated with nocturnal BP reduction). The absence of relationship between IOP and OPP in our study is also consistent with a recent study.[26]

To better characterize both groups of rhythm, associations between the type of rhythm and ocular or systemic factors have been analyzed. The group of patients with diurnal IOP acrophase was significantly associated with capillaropathy. Vascular dysregulation, such as migraine, tinnitus, and Raynaud's phenomenon have been reported to be associated with NTG.[9,10,40] This association has been reinforced in patients with NTG by the presence of a generalized peripheral vascular endothelial dysfunction,[41,42] reduced vasodilator responses to an endothelin A receptor antagonist in the forearms,[43] increased plasma and aqueous levels of endothelin 1,[44] an abnormal response of plasma endothelin 1 to temperature changes,[45] and low-basal flow velocities in the ophthalmic arteries.[46]

In addition to capillaropathy, 81% of patients with NTG had a diagnosis of OSAS (13/16 patients studied with polysomnography in the totality of our population). The role of OSAS in the development of NTG has been recently discussed.[47,48] However, our results should be confirmed by further studies, since no control population was studied and bias selection may have occurred. In patients with OSAS, the sympathetic activity has been reported to increase,[49] with an absence of reduction of BP during the night or an increase of nocturnal BP. The high prevalence of OSAS in our study may explain the proportion of non- or reverse dippers (87.5%). Night hypertension is also now accepted as being associated with target damage and predicting as well as sustained hypertension cardiovascular morbidity.[50] Further common factors of NTG and OSAS are the endothelial dysfunction[51] as discussed earlier and the production of endothelin 1.[52]

The average mean BP found in our series (94.7 ± 11.7 mm Hg) is consistent with that found in a large study of NTG (92 ± 10 mm Hg).[11] Several vascular parameters have been implicated in the NTG, such as a greater variability of nocturnal BP,[38] the alteration of nocturnal BP reduction,[7] and an association between nyctohemeral mean OPP fluctuation and nocturnal BP reduction.[11] The physiological nocturnal BP reduction, referred to as a dip in BP and present in about two thirds of the normal population,[53] is caused by a nocturnal reduction of the sympathetic activity (reduced amount of the catecholamine circulating hormones). The remaining individuals are classified as reverse dippers, nondippers, or overdippers,[12,21] possibly associated with sympathetic dysfunction. These patients are at increased cardiovascular risk of development of end-organ damage.[50] Our population was characterized by the presence of a physiological dip in only 18.2% of the patients, which could be explained by the high proportion of OSAS. In contrast with previous studies,[8,26] we did not find that patients with NTG exhibited a marked nocturnal BP reduction (only 4.5% of extreme dippers). The mean percentage decrease in BP, either systolic (27%) or diastolic (34%), was lower than that found by Hayreh et al.,[7] who reported a 37% and 47.8% decrease, respectively. However, the relationship between dips and NTG development remains controversial[12,54,55] and the fact that most studies, including ours, included patients with treated systemic hypertension[56–58] may introduce a bias, in that treatment of hypertension causes nocturnal dips in BP.

IOP and BP was measured the same day to calculate OPP and to correlate as precisely as possible both rhythms. Indeed acute variations of BP may have a significant effect on IOP.[59] Other authors have reported the measurement of BP and IOP on separate days to prevent the IOP measurement process from affecting the BP readings.[34] This issue was not considered in our experiment, since arterial pressure was measured just before IOP reading. Given that BP is measured every 15 minutes during the day and every 30 minutes during the night, it seems unlikely that IOP measurements may have consequences on BP 15 or 30 minutes after. On the other hand, there are several studies[47,60,61] that outlined the significant intrasubject variability in the diurnal fluctuations in BP and dipper status, which may in part reflect day-to-day variations in sleep disturbance and dailies activities. This last point probably explains why most studies which reported IOP and BP data had measurements performed the same day.[6,11,26,41,62]

Another difficulty in comparing studies may be related to the different definitions of the nocturnal dip, as a decrease of BP between 5% and 10%[26] or between 10% and 20% (our study).[12,20] This may also explain the lowest number of overdipper patients in our study compared with the number in a recent study.[26] If we applied the definitions of Choi et al.,[26] we would find 30% of overdippers and 20% of nondippers, compared with 4.5% and 54.6% in the present study, respectively.

In conclusion, three different populations of patients with NTG may be determined, according to their nyctohemeral rhythm of IOP. Methodological considerations emphasize the need of modeling IOP measurements and of a common definition of physiological dip of BP. This study reinforces the idea that pathophysiological mechanisms of NTG are multiple: abnormality of IOP (63%) and OPP (58%) rhythm, endothelial dysfunction or OSAS. A larger population is needed to confirm the association between IOP rhythm and visual field evolution and to confirm the association between OSAS and NTG.

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