

Frequent Loss of Nyctohemeral Rhythm of Intraocular Pressure Restored by nCPAP Treatment in Patients With Severe Apnea

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Objective: To assess 24-hour intraocular pressure (IOP) and ocular perfusion pressure rhythms in newly diagnosed apneic patients before and after nasal continuous positive airway pressure (nCPAP) treatment.

Methods: Intraocular pressure (using a Tonopen XL) and ambulatory blood pressure, measured hourly for 24 hours, were analyzed in 18 consecutive patients with obstructive sleep apnea for nyctohemeral rhythmicity (cosinor model). Twelve of 18 patients were reassessed after nCPAP use.

Results: Before treatment, 28% of the patients with obstructive sleep apnea demonstrated a nocturnal acrophase, 22% a diurnal acrophase, and 50% absence of 24-

hour rhythm of IOP. The ocular perfusion pressure rhythm was nocturnal in 78% of cases and absent in 22%. Using nCPAP, the mean (standard error of the mean) nocturnal IOP increased from 14.8 (0.8) to 18.3 (1.2) mm Hg ($P < .03$). Among patients with initial abnormal IOP rhythm (ie, rhythm with diurnal acrophase or absence of rhythm), 67% shifted to a normal 24-hour IOP profile after treatment.

Conclusions: Normal IOP nyctohemeral rhythm is lost in most patients with severe apnea. Nasal continuous positive airway pressure use restored a normal 24-hour IOP profile in most cases.

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IN HUMANS, INTRAOCULAR PRESSURE (IOP) is known to vary throughout the 24-hour period (nyctohemeral rhythm),^{1,2} with IOP higher during the night. Levels of IOP are influenced by hemodynamic parameters, autonomic function,³ posture,¹ and stage of sleep, IOP being lower during rapid eye movement and higher during slow-wave sleep.¹

Obstructive sleep apnea syndrome (OSA) is characterized by recurrent episodes of partial or complete upper airway obstruction during sleep. These pharyngeal collapses are nearly always associated with a desaturation-reoxygenation sequence that detrimentally stimulates the cardiovascular system. It has now been demonstrated that, even after adjustment for confounding factors, OSA per se is able to generate hypertension, atherosclerosis, and autonomic dysfunction,⁴ all conditions that may interact with IOP regulation. There are numerous factors capable of inducing acute or chronic changes in IOP in patients with apnea such as hemodynamic parameters, high sympathetic tone, and vigilance state. Obstructive respiratory events may be simulated by negative inspiratory efforts that are associated with huge variations in central venous pres-

sure and thus in IOP.⁵ Finally, slow-wave sleep, associated with the highest IOP values in healthy subjects,¹ is virtually abolished in severe OSA. Nasal continuous positive airway pressure (nCPAP), the first-line therapy for OSA, suppresses abnormal respiratory events to restore sleep quality and to reverse partly or completely acute and chronic cardiovascular modifications associated with the disease. Accordingly, the effect of nCPAP on the rhythm of IOP and ocular perfusion pressure (OPP) needs to be further evaluated.

In this context, we hypothesize that OSA and OSA treatment could influence the IOP and OPP nyctohemeral profile. The aim of our study was to assess 24-hour IOP and OPP rhythm in newly diagnosed patients with apnea before and after nCPAP treatment.

METHODS

POPULATION STUDIED

Eighteen white subjects (16 men, 2 women) agreed to participate in the investigation and gave their informed consent, in accordance with the tenets of the Declaration of Helsinki. Patients were consecutively included in our tertiary center. The study protocol was approved by the local institutional review board (IRB No. 6705).

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Patients were eligible if they had newly diagnosed sleep apnea based on polysomnography. Exclusion criteria were an ultrasound measurement of corneal thickness greater than 590 μm or less than 500 μm , refractive status greater than 2 diopters, an ocular disease such as ocular hypertension or glaucoma, optic neuropathy, retinal disease, diabetes mellitus, and taking drugs that are known to have a potential effect on IOP such as local or systemic steroids. Patients with systemic hypertension were included if the antihypertensive treatment was not modified during the study to minimize the potential effect of drugs on blood pressure and OPP during the study. In this series, the main medical histories were smoking ($n=3$), hypercholesterolemia ($n=5$), and treated systemic hypertension ($n=4$).

POLYSOMNOGRAPHY

Continuous recordings were taken with electrode positions C3/A2-C4/A1-Cz/01 of the international 10-20 Electrode Placement System, eye movements, chin electromyogram, and electrocardiogram with modified V2 lead. Sleep was scored manually according to standard criteria.⁶ Airflow was measured with nasal pressure associated with the sum of buccal and nasal thermistor signals. Respiratory effort was monitored with abdominal and thoracic bands. An additional indicator of respiratory effort (ie, pulse transit time) was recorded concurrently. Oxygen saturation was measured using a pulse oximeter (Biox-Ohmeda 3700, Ohmeda, Liberty Corner, New Jersey). A hypopnea episode was measured when a 50% reduction in nasal pressure signal (continuous recording of inspiratory and expiratory pressure) was associated with a 4% desaturation (4% drop in oxygen blood pressure [BP] from baseline) and/or a microarousal (abrupt shift in electroencephalogram frequency).⁷ Apneas were defined as a 10-second pause in respiration during sleep. Apneas were classified as obstructive, central, or mixed according to the presence or absence of respiratory efforts. The classification of hypopneas as obstructive or central was based on the pulse transit time signal and the shape of the respiratory curve of nasal pressure (flow-limited aspect or not). Sleep apnea was defined as an apnea-hypopnea index of 15 or more per hour.⁸ The American Academy of Sleep Medicine Task Force⁷ has proposed an apnea-hypopnea index of 30 events per hour to distinguish moderate from severe OSA.

The second polysomnography was done on nCPAP with patients wearing their mask during IOP measurements. Compliance with nCPAP was considered acceptable if the device was used at least 4 hours per night.⁹

AMBULATORY BP MONITORING

Ambulatory BP was monitored with a Diasys Integra device (Novacor SA, Rueil-Malmaison, France). The measurements were made every 15 minutes during the day and 30 minutes at night. The following ambulatory BP monitoring parameters were studied: systolic BP (SBP), diastolic BP (DBP), mean BP (MBP), and heart rate (HR). Values of MBP were averaged per hour, according to the formula $\text{MBP} = \text{DBP} + 1/3 \times (\text{SBP} - \text{DBP})$. Nocturnal BP reduction was calculated as $100 \times (1 - \text{sleep SBP} / \text{awake SBP})$. We classified the patients as nocturnal dippers if the nocturnal BP fall was 10% or more but less than 20%.¹⁰

OPHTHALMIC EXAMINATION, IOP MEASUREMENTS, AND MEAN OPP CALCULATION

Each patient answered a questionnaire on their ocular history and had a complete ocular examination (visual acuity, slit-lamp examination, IOP measurement with a Goldmann to-

nometer, gonioscopy, and funduscopy). The eye examination was completed by visual field tests (Humphrey 24/2 and 10/2 SITA-standard visual field) and a color vision test (Farnsworth-Munsell 100 Hue test). Results of ocular examination of all subjects were normal.

Intraocular pressure was measured hourly during the 24-hour period by a single examiner with the Tonopen XL, as previously described,^{1,11,12} which allowed measurements in all positions.

For experimental sessions, the subjects were housed in a sleep laboratory for 24 hours in a strictly controlled environment (sitting position from 8:00 AM to 8:59 PM and supine position from 9:00 PM to 7:59 AM, light cycle according to the sleep/wake cycle of each patient, temperature, fluid intake, and meals)¹² with continuous monitoring of sleep. Patients were authorized to sleep at their habitual hours. Hourly IOP measurements started at 8:00 AM and were taken for 24 hours on the right eye after the instillation of a contact anesthetic (Oxybutyprocaine, Novartis Pharma Rueil-Malmaison). At night, the subjects were awakened hourly for IOP measurement, remaining in bed in supine position.

Ocular perfusion pressure¹³ was calculated as follows: $\text{OPP}_{\text{sitting position}} = (95/140 \times \text{MBP}) - \text{IOP}$ from 8:00 AM to 8:59 PM and $\text{OPP}_{\text{lying position}} = (115/130 \times \text{MBP}) - \text{IOP}$ from 9:00 PM to 7:59 AM.

STATISTICAL ANALYSIS

The nyctohemeral rhythm of IOP was tested through the cosinor model for biological rhythms, represented by the best fitting sine curve following the data points.¹ An analysis of variance was used to calculate factor F and determine if the rhythm was sinusoidal-like or if there was no rhythm. The characteristics of the circadian rhythm were expressed as mesor (mean 24-hour value) and acrophase (the time at which the highest value encountered in the cycle occurs). An IOP rhythm was defined as a diurnal (ie, between 8:00 AM and 8:59 PM) or nocturnal rhythm according to the time of the acrophase.^{1,14} Absence of nyctohemeral IOP rhythm was reported if the cosinor analysis showed a factor F of less than 3.47.¹

All values are mean (standard error of the mean). When variables were not normally distributed, nonparametric tests were used. The Mann-Whitney *U* or Kruskal-Wallis tests were used for between-group comparisons. To compare values before and after nCPAP, the Wilcoxon or the paired *t* test were used. The number of patients included in this study ($n=18$) was calculated assuming the following hypothesis of IOP rhythm being abnormal (ie, rhythm with diurnal acrophase or absence of rhythm) in 90% of the cases before treatment and 30% after nCPAP, an α risk of 5%, and a power of 80%. Significance was accepted as $P < .05$.

RESULTS

PRETREATMENT DATA

The anthropometric, sleep, IOP, and BP data are presented in **Table 1**. Patients were obese, middle-aged, and had severe apnea. For the whole group, 24-hour mean IOP values were within the reference range.

Following 24-hour IOP variation analysis, patients were classified as having diurnal IOP rhythm (diurnal acrophase), absence of IOP rhythm, or nocturnal IOP rhythm (nocturnal acrophase). At the time of diagnosis (Table 1; **Figure 1** and **Figure 2**), only 5 of 18 patients (28%) demonstrated a healthy IOP circadian rhythm (ie, with

Table 1. Anthropometric, Sleep, and Ambulatory BP and Ocular Data of the 18 Patients With OSA Syndrome

	Mean (SEM)				P Value ^a
	All Patients (N=18)	IOP Nyctohemeral Rhythm With Diurnal Acrophase (n=4; 22%)	Absence of IOP Nyctohemeral Rhythm (n=9; 50%)	IOP Nyctohemeral Rhythm With Nocturnal Acrophase (n=5; 28%)	
Individual characteristics					
Age, y	50 (2)	48 (9)	53 (3)	46 (3)	.43
BMI	32.5 (1.0)	30.0 (1.2)	32.7 (1.5)	34.2 (1.8)	.32
Sex, No.					.64
Male	16	4	8	4	
Female	2	0	1	1	
Polysomnographic data					
Total sleep time, min	344 (12)	341 (25)	345 (20)	346 (22)	.99
Stage 3-4 sleep, % of total sleep time	6.2 (6.9)	9.3 (3.9)	5.1 (2.5)	5.2 (3.0)	.61
Apnea and hypopnea index, No./h of sleep	62.6 (7.2)	39.5 (9.6)	66.6 (11.1)	73.8 (11.9)	.22
Mean nocturnal SaO ₂ , %	92 (1)	95 (2)	91 (1)	91 (2)	.17
Minimal nocturnal SaO ₂ , %	77 (3)	88 (2)	76 (4)	71 (4)	.08
Microarousal index, (No./h of sleep)	57.9 (5.5)	42.6 (5.6)	60.6 (9.5)	65.1 (7.8)	.33
IOP over 24 h					
Mesor, mm Hg (24-h values)	14.9 (0.5)	15.5 (1.0)	14.4 (0.6)	15.4 (1.1)	.57
Acrophase, h ^b	7.2 (1.5)	11.5 (1.0)	NA	3.8 (0.9)	.01
Acrophase IOP, mm Hg ^b	18.4 (0.5)	18.8 (0.8)	NA	18.2 (0.7)	.80
Diurnal IOP, mm Hg	14.8 (0.5)	17.0 (0.8)	14.3 (0.6)	14.1 (1.1)	.09
Nocturnal IOP, mm Hg	15.0 (0.7)	13.4 (1.8)	14.4 (0.7)	17.2 (1.2)	.08
OPP					
Mesor, mm Hg (24-h values)	65.3 (1.4)	61.4 (3.2)	67.4 (1.8)	65.4 (2.6)	.24
Acrophase, h	2.6 (0.1)	2.4 (0.1)	2.7 (0.2)	2.6 (0.4)	.48
Acrophase OPP, mm Hg	9.3 (1.6)	14.0 (4.0)	6.7 (0.6)	8.0 (0.0)	.11
Acrophase, %					
Absence of rhythm	22	0	22	40	.18
Diurnal	0	0	0	0	
Nocturnal	78	100	78	60	
Diurnal OPP, mm Hg	59.0 (1.2)	55.0 (2.1)	59.7 (0.9)	61.6 (3.1)	.10
Nocturnal OPP, mm Hg	74.1 (2.3)	70.4 (4.9)	78.2 (3.6)	70.6 (2.2)	.27
Ambulatory BP, mm Hg					
24-h SBP	129 (2)	127 (3)	131 (3)	128 (4)	.62
24-h DBP	83 (2)	78 (4)	85 (2)	81 (4)	.35
Night SBP	123 (3)	120 (3)	126 (5)	124 (5)	.71
Night DBP	79 (3)	74 (5)	83 (4)	79 (6)	.47
Day SBP	132 (3)	130 (3)	130 (5)	137 (5)	.52
Day DBP	85 (2)	81 (3)	86 (2)	89 (4)	.21
Nocturnal dippers, No. (%)					
Yes	6 (33)	2 (50)	2 (22)	2 (40)	.58
No	12 (67)	2 (50)	7 (78)	3 (60)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DBP, diastolic blood pressure; IOP, intraocular pressure; NA, not applicable; OPP, ocular perfusion pressure; OSA, obstructive sleep apnea; SaO₂, arterial oxygen saturation; SBP, systolic BP; SEM, standard error of the mean.

^aAnalysis of variance or Mann-Whitney *U* test.

^bAcrophase data could not be calculated in the subgroups of patients with an absence of IOP (n=9) or OPP (n=4) rhythm.

a nocturnal acrophase). Nine of 18 patients (50%) did not exhibit any circadian IOP variation. A diurnal rhythm was found in 4 patients (22%). The OPP rhythm was nocturnal in 14 of 18 patients (78%) and was absent in 4 of 18 patients (22.2%; Table 1).

nCPAP EFFECT ON IOP AND OPP

Twelve of the 18 patients with OSA were reassessed after a minimum of 1 month and 6.7 (2.4) months of nCPAP use (n=12; nCPAP compliance=3.6 [0.7] h). Three patients did not use their nCPAP device at all at home before the investigation.

This population did not significantly differ from the initial population in terms of anthropometrics or sever-

ity of sleep apnea. As expected, sleep apnea was alleviated by nCPAP (Table 2), as demonstrated by the apnea-hypopnea index, to fewer than 10 events per hour (3.8±1.2/h). Treatment with nCPAP also allowed an increase in slow-wave sleep, a substantial reduction in sleep fragmentation, and significantly reduced BP during the day (Table 2). In relation with nCPAP treatment, the nocturnal IOP increased significantly from 14.8 (0.8) to 18.3 (1.2) mm Hg. The peaks of IOP during the 24-hour period before nCPAP (20.5 [0.6] mm Hg; range, 17-24 mm Hg) and after nCPAP (22.6 [1.2] mm Hg; range, 16-32 mm Hg) were similar (P=.2). Among patients with initial abnormal IOP rhythm (9 of 12), 67% (6 of 9) shifted to a normal IOP 24-hour profile when using nCPAP (Figure 2). In 3 patients with OSA who were noncom-

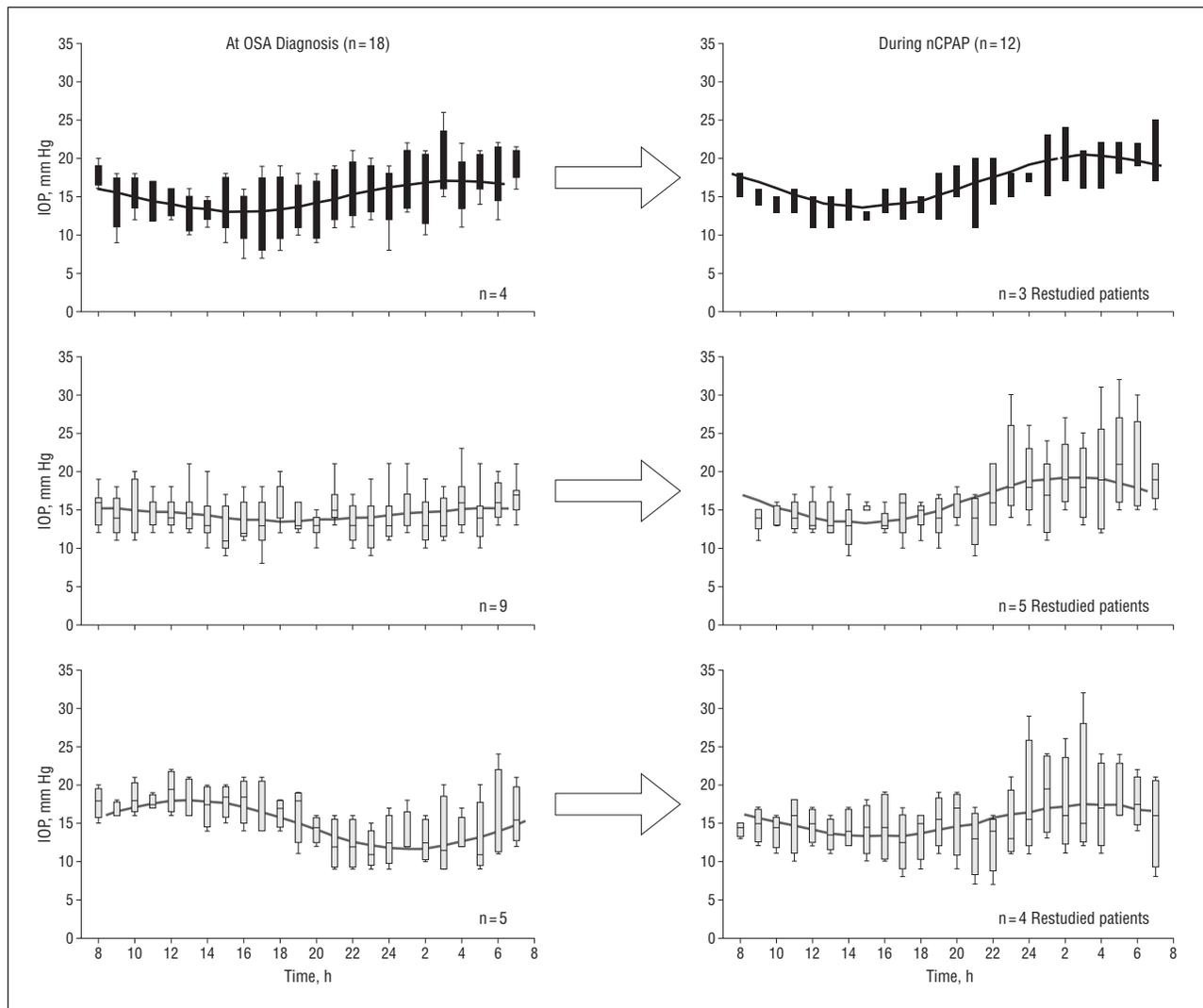


Figure 1. Curves of mean (standard error of the mean) intraocular pressures (IOPs) before and during nasal continuous positive airway pressure (nCPAP) treatment of patients with obstructive sleep apnea (OSA). A, At diagnosis, patients had normal IOP nyctohemeral rhythm (nocturnal acrophase); all 3 patients reassessed after treatment continued to have normal IOP rhythm. B, At diagnosis, patients did not have IOP nyctohemeral rhythm; of 5 patients reassessed after treatment, 3 had normal IOP rhythm and 2 no IOP rhythm. C, At diagnosis, patients had IOP nyctohemeral rhythm and diurnal acrophase; of 4 patients reassessed after treatment, 3 had normalized rhythm. The box plot represents the quartiles, extremes, and the median values. The solid line illustrates the fit of the mean IOP data over 24 hours.

pliant with nCPAP at home and had inverted IOP rhythm ($n=1$) or absence of rhythm ($n=2$), 1 night of nCPAP use in the sleep laboratory was sufficient to restore a nyctohemeral IOP rhythm in 2 of 3 cases.

After nCPAP (Table 2), the OPP rhythm was nocturnal in 42% of the patients, with no detected nyctohemeral rhythm in 58% of the cases. The rhythm was shifted from absence of rhythm to nocturnal rhythm in 1 case, from nocturnal to absence of rhythm in 5 cases, and unchanged in 6 cases. Finally, there was a trend for a reduction of OPP during the night ($P=.07$).

COMMENT

The most important finding of this study was that less than 30% of the 18 patients with severe OSA exhibited a normal nyctohemeral IOP profile at baseline. These patients showed a normal nyctohemeral OPP profile in 78% of the cases. All but 3 of the 12 nCPAP-treated patients

(75%) had a normal nyctohemeral IOP profile. The main change when using nCPAP was a significant increase in IOP during the night, associated with a trend toward daytime and nighttime OPP reduction.

Several methodological points need consideration for the interpretation of nyctohemeral IOP data. The methodology of the study was unique, with IOP measurements every hour in a physiological posture (sitting during the day and supine at night)^{12,15-17} and in controlled environmental conditions (lighting, meals, activity). Hourly measurements made it possible to model the rhythms significantly more precisely and meaningfully^{1,11,12} and calculate the acrophase and subsequently classify rhythms as diurnal or nocturnal. This approach is crucial because it is methodologically inappropriate to pool IOP data from different groups of patients with different rhythms; this is because mean profiles would not reflect true individual variations across the day but would represent the average of the low values of some eyes with the high values mea-

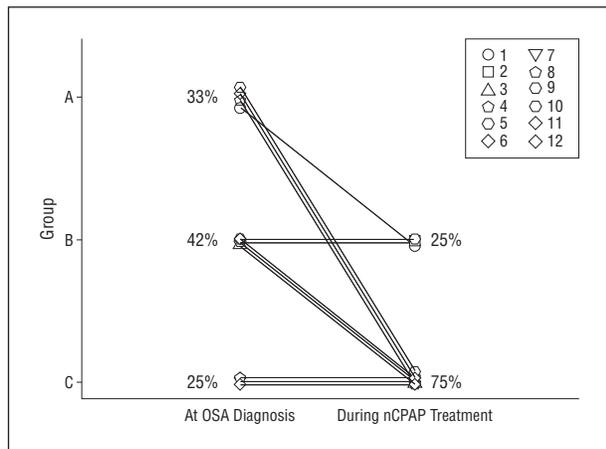


Figure 2. Distribution of patients with obstructive sleep apnea (OSA) before and under nasal continuous positive airway pressure treatment (nCPAP) treatment. Group A consisted of patients with intraocular pressure (IOP) nyctohemeral rhythm and diurnal acrophase (n=4); group B, patients without IOP nyctohemeral rhythm (n=5); and group C, patients with normal (nocturnal acrophase) IOP nyctohemeral rhythm (n=3).

sured for other eyes. Hence, mean calculations are suitable only in patients who have been previously classified in homogeneous groups of IOP rhythms.

The effect of IOP measurements on sleep quality and BP measurements also needs to be considered. The duration of IOP measurements was reduced as much as possible, and in these patients with severe OSA with a mean sleep fragmentation index of 60/h, IOP measurements should not interfere significantly on sleep quality. The IOP and BP were measured the same day to calculate OPP and to correlate the 2 rhythms as precisely as possible.

Many factors may explain an abnormal IOP rhythm in OSA and normalization (ie, rise in IOP during the night) when using nCPAP. Potential factors are those disturbed by OSA, normalized when using nCPAP, and known to influence IOP regulation. These factors may also affect IOP variations during the day and night differently. As reported recently,¹⁸ nCPAP induces an IOP increase during night, with a mean difference in IOP between night and day in our series reaching approximately 3.5 mm Hg. Kiekens et al¹⁸ attributed these IOP changes mainly to the nCPAP device. In our study, this nocturnal IOP increase was essentially reported for 4 of the 5 patients with any detectable rhythm, in 2 of 3 patients with a normal IOP rhythm, and in 2 of the 4 with an initial inversed rhythm. Finally, the nocturnal IOP increase was essentially noted for patients who normalized their IOP rhythm. No patient had an IOP of more than 25 mm Hg before nCPAP and 2 patients did after nCPAP, which is significantly less than in a previous study¹⁸ with at least 24% of the patients (5 of 21) having a highest IOP greater than 25 mm Hg after nCPAP. Finally, our interpretation of both Kiekens and colleagues' results and our series is that nCPAP acts principally by restoring the normal nocturnal IOP acrophase. This is a crucial point in clinical practice because the dangers of CPAP can be discarded; our interpretation is that nCPAP participates in restoring a normal IOP rhythm.

Factors that have a prominent effect during sleep and factors acutely sensitive to nCPAP application may in-

Table 2. Anthropometric, Sleep, and Ambulatory BP and Ocular Data of the 12 Patients With OSA Recorded Before and During nCPAP

	Mean (SEM)		P Value ^a
	No nCPAP	nCPAP	
Individual characteristics			
BMI	31.6 (1.0)	31.4 (1.0)	.50
Polysomnographic data			
Total sleep time, min	356 (15)	356 (7)	.98
Stage 3-4 sleep, % of total sleep time	6.3 (2.0)	13.4 (2.2)	.01
Apnea and hypopnea index, No./h of sleep	62.5 (7.9)	3.8 (1.2)	<.001
Nocturnal SaO ₂ , %	92.8 (1.0)	95.5 (0.5)	.02
Minimal nocturnal SaO ₂ , %	79 (3.0)	87 (2.0)	.02
Microarousal index, No./h of sleep	57.6 (6.0)	7.1 (1.5)	<.001
IOP data, mm Hg			
Mesor	15.2 (0.6)	15.9 (0.7)	.37
Acrophase, %			
Absence of rhythm	42	25	.01
Diurnal	33	0	
Nocturnal	25	75	
Diurnal IOP, mm Hg	15.4 (0.7)	14.3 (0.5)	.16
Nocturnal IOP, mm Hg	14.8 (0.8)	18.3 (1.2)	.03
OPP data, mmHg			
Mesor	64.5 (1.5)	60.5 (1.6)	.06
Acrophase, %			
Absence of rhythm	25	58	.10
Diurnal	0	0	
Nocturnal	75	42	
Diurnal OPP, mm Hg	58.9 (1.4)	56.6 (1.6)	.11
Nocturnal OPP, mm Hg	72.4 (2.3)	65.9 (2.1)	.07
Heart rate frequency, bpm			
24-h Value	73.5 (3.5)	71.8 (3.0)	.34
Diurnal	76.9 (3.6)	75.1 (3.1)	.28
Nocturnal	66.1 (3.3)	64.3 (2.9)	.91
Ambulatory BP monitoring, mm Hg			
24-h SBP	129 (2)	125 (2)	.04
24-h DBP	84 (2)	79 (2)	.005
Day SBP	132 (3)	127 (2)	.01
Day DBP	85 (2)	80 (2)	<.001
Night SBP	123 (3)	121 (2)	.12
Night DBP	79 (3)	77 (3)	.13
Nocturnal dippers, No. (%)			
Yes	4 (33)	2 (17)	.06
No	8 (67)	10 (73)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); bpm, beats per minute; DBP, diastolic blood pressure; IOP, intraocular pressure; nCPAP, nasal continuous positive airway pressure; OPP, ocular perfusion pressure; OSA, obstructive sleep apnea, SBP, systolic BP.

^aPaired *t* test or Wilcoxon rank sum test.

clude sleep stages, respiratory effort during sleep, dehydration, plasmatic atrial natriuretic peptide concentrations, and sympathetic tone. These factors are expected to induce lower IOP values in untreated OSA and be associated with an IOP increase during nCPAP treatment. Slow-wave sleep, a period accompanied by the highest IOP values during sleep in healthy individuals,^{1,11} is classically reduced in severe OSA, as in our patients (Table 1), and is partially restored by nCPAP use (from 6% to 13% of total sleep time in our group). This significant in-

crease in slow-wave sleep during nCPAP may participate in the nightly IOP increase during treatment. Respiratory effort, associated with a dose-dependent decrease in IOP,⁵ is also normalized by nCPAP use.¹⁹ Nocturnal dehydration and its associated rise in hematocrit occur in patients with OSA owing to increased diuresis during sleep that is attributed to an increased release of atrial natriuretic peptide.²⁰ Atrial natriuretic peptide secretion during sleep, nocturia, and hematocrit level can be normalized by 1 night of nCPAP treatment.²¹ These factors, such as dehydration¹⁵ and atrial natriuretic peptide elevation, are known to lower IOP in normal humans.²²

Influencing factors that have a persistent effect during the day and are sensitive to long-term nCPAP application may include sympathetic tone, renin-angiotensin-aldosterone system activity, and the CPAP-associated, long-lasting changes in BP. Daytime sympathetic tone is increased in untreated patients with OSA. Stimulation of the ocular β -adrenergic receptors by elevated circulating catecholamines and by norepinephrine released from the ocular sympathetic nerves may contribute to IOP regulation²³ via variations in aqueous outflow resistance (by α 1-adrenergic receptors) and aqueous production (partly by β -adrenergic receptors).²⁴ During the day, electrical stimulation of the cervical sympathetic nerves increases IOP in rabbits.²⁵ Use of nCPAP reduces the sympathetic activity found in patients with OSA,^{26,27} ie, it lowers BP, heart rate, and noradrenaline plasma levels.²⁸ This may contribute to the daytime IOP and BP reduction that we found in the present study. The activity of the renin-angiotensin-aldosterone system, which is enhanced in OSA²⁹ and implicated in IOP regulation via the type 1 angiotensin receptor,³⁰ may also be normalized by nCPAP, and this could participate in the daytime reduction in IOP.

Simultaneously with IOP changes, BP modifications lead to OPP changes. A previous study of healthy humans³¹ showed that OPP is normally higher during the night in real-life situations (ie, sitting position during the day and supine position during the night). Our study showed for the first time that the OPP rhythm may be disturbed in patients with OSA, with an absence of detected rhythm in 20% of cases. This absence of OPP rhythm is associated with a mean 12% and 13% reduction of systolic and diastolic BP during the night, respectively. On average, we did not find a significant reduction in DBP during the night after nCPAP, as recently described,¹⁸ but a significant reduction in SBP during the day (4 mm Hg). A mean 7% reduction in BP was only found in 6 of 8 patients with no OPP rhythm after nCPAP. As described in a recent study,¹⁸ we found a trend toward a decrease in OPP (around 9%) when patients were treated with nCPAP, especially during the night. In our study, this decrease may be a combination of the IOP increase and a slight but nonsignificant mean decrease in BP during the night. When analyzed in the subgroups of 12 treated patients with OSA, a nocturnal rhythm of OPP was observed in 9 of 12 patients (75%) before nCPAP compared with 42% after nCPAP. A 10% reduction in OPP and/or the loss of a nocturnal OPP rhythm may have an effect on ocular blood flow. Experiments using laser Doppler flowmetry of the optic nerve previously showed a certain degree of autoregulation when OPP decreases sec-

ondary to an IOP increase^{32,33} or a decrease in BP.³⁴ This autoregulation, which keeps the blood flow nearly constant despite the challenge of reduced vascular perfusion pressure, needs to be further studied in patients with OSA, especially at the level of the optic nerve.

There is a loss of the normal IOP nyctohemeral rhythm in most patients with severe apnea. Acute and chronic nCPAP use is associated with a return to a normal 24-hour IOP profile in most cases. Further studies are needed to investigate how IOP and OPP changes influence microvascularization in the optic nerve. Our study demonstrates that IOP changes induced by nCPAP are explained by restoring normal IOP rhythm rather than by a deleterious effect of the device.

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Ophthalmic Images

Acute Macular Neuroretinopathy

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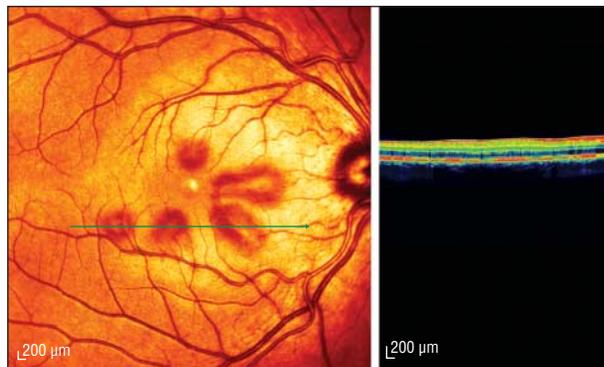


Figure 1. Spectral domain optical coherence tomography demonstrating the characteristic lesions of acute macular neuroretinopathy. The lesions in the outer segment of the photoreceptor layer are displayed by the loss of reflectivity seen here.

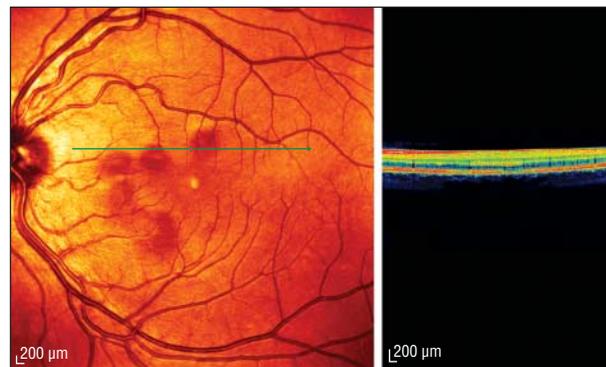


Figure 2. The hallmark lesions have been described as dark red to brown and wedge or oval shaped, arranged in a "flower petal" pattern and directed toward the fovea.