Continuous Positive Airway Pressure Therapy Is Associated with an Increase in Intraocular Pressure in Obstructive Sleep Apnea

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PURPOSE. Several reports have demonstrated an association between glaucoma and obstructive sleep apnea (OSA), though the origin of this association remains unknown. In the present study, the influence of OSA and continuous positive airway pressure (CPAP) therapy on intraocular pressure (IOP) and ocular perfusion pressure (OPP) was examined.

METHODS. IOP, blood pressure, and pulse rate were measured every 2 hours during 24-hour sessions in 21 patients with newly diagnosed OSA. A first series of measurements was performed before CPAP therapy, and a second series was performed 1 month after the initiation of CPAP therapy. OPP was then calculated.

RESULTS. Baseline measurements showed a significant nycthemeral fluctuation in the average IOP, with the highest IOPs at night. After 1 month of CPAP therapy, the average IOP was significantly higher. A 24-hour IOP fluctuation of ≥8 mm Hg was found in 7 patients at baseline and in 12 patients during CPAP therapy. The mean difference between trough and peak IOP was 6.7 ± 1.5 mm Hg at baseline and 9.0 ± 2.0 mm Hg during CPAP therapy. Thirty minutes after CPAP cessation a significant decrease in IOP was recorded. There was a statistically significant decrease in mean OPP during CPAP therapy.

CONCLUSIONS. Patients with OSA demonstrated significant 24-hour IOP fluctuations, with the highest values at night. CPAP therapy causes an additional IOP increase, especially at night. Regular screening of visual fields and the optic disc is warranted for all patients with OSA, especially those treated with CPAP.

Glaucoma is defined as a chronic progressive optical neuropathy with irreversible visual field defects and excavation of the optic nerve head. Elevated intraocular pressure (IOP) and cardiovascular disease are the main risk factors in the development and progression of glaucoma.

As IOP is influenced by different (patho)physiological factors, studying the circadian IOP course in OSA could help explain the higher prevalence of glaucoma in OSA.

We analyzed the 24-hour IOP course in patients with newly diagnosed OSA in baseline conditions and 1 month after onset of CPAP therapy. We also analyzed the immediate effects of both CPAP application and acute CPAP withdrawal on nocturnal IOP.

Blood pressure and pulse rate were also recorded since vascular perfusion problems play an important role in glaucomatous neuropathy and are more frequent in OSA.

METHODS

Patients

Twenty-one patients with newly diagnosed OSA, in whom CPAP therapy was indicated (apnea-hypopnea index [AHI] > 20 and microarousal index [MAI] ≥ 30), were recruited consecutively within 1 month. They all agreed to participate voluntarily in our project and gave their informed consent. This study was approved by our institutional ethics committee and adhered to the standards of the Declaration of Helsinki.

Of the 18 men and 3 women, aged 40 to 76 years, 11 patients had no medical history. Of the five patients with diabetes mellitus, four patients had cardiovascular antecedents including arterial hypertension, cardiac valve replacement, coronary artery bypass graft, and atrial fibrillation, as did five other patients. Ocular diagnoses included diabetic retinopathy (four patients), which was treated with retinal photocoagulation (two patients). One patient had normal-tension glaucoma with a vertical cup-disc ratio of 0.9 and visual field defects. None of the 20 other patients with newly diagnosed OSA had a glaucomatous disc or suspect visual field defects.

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Inclusion criteria were older than 18 years, newly diagnosed, untreated OSA with indications for CPAP use, no or mild refractive errors, and a normal anterior chamber with an open angle.

Exclusion criteria included any abnormality that prevented reliable applanation tonometry, intraocular conventional surgery or laser surgery within the past year, and previous glaucoma surgery or refractive surgery. The patient’s characteristics are shown in Table 1.

### Polysomnography

Diagnosis of OSA was based on polysomnography with simultaneous recording of EEG, EMG, EOG, oronasal flow, ribcage and abdominal movements, ECG, oxygen saturation, and body position (Sleep Disorders Center, Antwerp University Hospital). Data were analyzed with a semiautomated system (Oxford Medilog SAC, Oxford Instruments, Oxford, UK), allowing additional visual scoring. Arousals were scored based on the AWDMA criteria, and the MAI was calculated.15 Apnea was defined as an interruption of the oronasal airflow. Hypopnea was defined as a reduction in airflow with a 50% reduction in thoracic and abdominal efforts for at least 10 seconds and a 3% drop in oxygen saturation from the preceding stable or arousal. The AHI was the sum of the number of apneas and hypopneas per hour of sleep. CPAP titration was performed during polysomnography to determine the optimal CPAP pressure. Pulmonary function tests were obtained with the patient in a standing position and breathing room air. Forced spirometry was performed with a pneumotachograph (Alveo-Diffusiontest; Jaeger, Wurzburg, Germany). Lung volumes and airway resistance were determined with body plethysmography (Bodytest; Jaeger). Blood gases were processed immediately in an analyzer.

### Ophthalmic Evaluation and Measurements

Every patient had an ophthalmic examination consisting of medical history, best-corrected visual acuity, slit lamp biomicroscopy, funduscopy, gonioscopy, pachymetry, and visual field analysis (Humphrey Field Analyzer; Sita Standard 24-2, Rev A1.1; Carl Zeiss Meditec, Dublin, CA). Patients with glaucoma were defined as having glaucomatous optic disc changes or repeatable glaucomatous visual field defects. Abnormal discs were defined as those having large excavation, focal rim defects, hemorrhage, notching, nerve fiber layer defects, or cup-disc ratio asymmetry between both eyes of 0.2 or more. An abnormal visual field was determined by clinical review and by the manufacturer’s criteria for abnormality (Statpac; Full-Threshold 24-2 examination; Carl Zeiss Meditec). IOP measurement was performed with a Perkins handheld applanation tonometer (Clement Clarke, Harlow, UK), after instillation of an anesthetic oxybuprocaine hydrochloride 0.4% eye drop (Unicare®; Thea, Schaffhausen, Germany) followed by fluorescein staining. Every 2 hours, at least two measurements of the left eye and two measurements of the right eye were performed, to obtain an average IOP. The average of both IOPs was recorded. If the two measurements differed more than 2 mm Hg, a third measurement was performed. All IOP measurements were taken by the same ophthalmologist (VDG).

### Statistical Analysis

All data are expressed as the mean ± SEM. Normal distribution of all parameters was confirmed with a Kolmogorov-Smirnov test. Statistical analysis for repeated measures was performed with MANOVA (SPSS 12.0; SPSS, Chicago, IL) to evaluate the effect of CPAP on IOP, blood pressure, pulse rate, and OPP.

Pearson correlation analysis was performed between peak IOP, IOP difference between lowest and highest value (diurnal fluctuation), body mass index (BMI), neck circumference, AHI, MAI, Epworth sleepiness scale, pachymetry, and CPAP. To evaluate the effect of sleep position (dorsal or lateral decubitus) on IOP, MANOVA was used. Normal distribution was confirmed with a Kolmogorov-Smirnov test.

### Results

The average 24-hour IOP graph at baseline showed a cyclic pattern (Fig. 1), with the lowest IOP measurements between 2 and 10 PM and the highest IOPs at night. Nycthemeral fluctuations in the average IOP at baseline were statistically significant (Pillai’s trace = 0.87, F(11,9) = 5.7, P < 0.05). Contrast tests (in comparison with the latest IOP measurement at 10 AM) showed significantly lower IOP at 2, 4, 6, and 10 PM.

One month after onset of CPAP therapy, the average IOP (Fig. 1) was significantly higher than baseline (Pillai’s trace = 0.28, F(11,9) = 7.5, P < 0.05). The overnight IOP increase due to CPAP was even more pronounced compared with baseline (significant interaction effect between CPAP treatment and time of measurement) (Pillai’s trace = 0.92, F(11,9) = 9.14, P < 0.05). A contrast test showed a statistically significant difference in IOP between the two sessions at 2, 4, 6, and 8 AM.

### CPAP-Related IOP Increase in Sleep Apnea

Systemic blood pressure and pulse rate were recorded manually at the same time by one person (SK). Blood flow in any tissue is generated by its perfusion pressure. The ocular perfusion pressure (OPP) is the pressure that forces blood to flow through the ocular vascular bed and is equal to the difference between the mean arterial pressure and the venous pressure at the exit point. The venous pressure in the eye is approximately equal to the IOP. The OPP was calculated based on IOP, systolic blood pressure (SBP), and diastolic blood pressure (DBP), according to ophthalmodynamometric studies (subtracting the IOP [as a substitute for venous pressure] from two thirds of the mean arterial pressure [result of DBP plus one third of the difference between SBP and DBP]).16

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

### Study Design

In this prospective study, the patients were evaluated during two sessions of 24 hours: a first session at baseline, and a second session 1 month after initiation of CPAP therapy. During each 24-hour session, starting at noon and ending at 10 AM the next day, IOP and vascular parameters were measured every 2 hours in supine position, so that the same registration method was used during daytime and nighttime. The patients were encouraged to continue normal daily activities. At 7 PM they were allowed to enter their rooms. A lunch was offered between noon and 2:00 PM, dinner was served at 7:00 PM and breakfast at 8:30 AM.

At night, the patients were awakened and instructed to stay supine in bed. If the patient was not in the dorsal decubitus position before awakening, the former posture was noted to evaluate its influence on IOP. Patients’ exposure to light was minimized. After a short period of awakening, the patients were allowed to continue sleeping.

During the second session, the CPAP mask remained applied during the overnight measurements. Immediately after CPAP cessation in the morning, the patients were asked to remain supine. Thirty minutes later, IOP was measured to evaluate the effect of acute CPAP withdrawal.

### Table 1. Characteristics of Patients with OSA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>57 ± 2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31 ± 2</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>43 ± 1</td>
</tr>
<tr>
<td>Diabetes (% of total group)</td>
<td>19</td>
</tr>
<tr>
<td>Epworth sleepiness scale (1-24) score</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>AHI (n/h)</td>
<td>48 ± 5</td>
</tr>
<tr>
<td>MAI (n/h)</td>
<td>53 ± 5</td>
</tr>
<tr>
<td>CPAP pressure (cm H₂O)</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>AHI during CPAP titration night (n/h)</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>Corneal thickness (µm)</td>
<td>541 ± 8</td>
</tr>
</tbody>
</table>

n = 21.
whereas no significant difference in IOP was found at all other time points.

An overview of the highest IOPs and the number of patients with IOP rising above 25 mm Hg is given in Table 2. A 24-hour IOP fluctuation of ≥8 mm Hg was found in 7 patients at baseline and in 12 patients during CPAP therapy. The mean of all trough-peak differences in IOP was 6.7 ± 1.5 mm Hg at baseline and 9.0 ± 2.0 mm Hg during CPAP therapy.

A statistically significant decrease in the mean IOP was found 30 minutes after CPAP withdrawal from 20.8 ± 1.0 to 18.6 ± 0.7 mm Hg (Pillai's trace = 0.47, F(1,100) = 15.7, P < 0.05; Fig. 2). No significant variations were found in systolic blood pressure (SBP) at baseline, nor during CPAP therapy (Fig. 3). A statistically significant difference in diastolic blood pressure (DBP) was observed during CPAP therapy, compared with baseline (significant interaction effect between CPAP treatment and time of measurement (Pillai's trace = 0.93, F(11,9) = 4.1, P < 0.05). A contrast test showed higher values at noon, 2, 4, and 6 PM (Fig. 4).

Significant fluctuations of pulse rate during the nychthemeron were found (Pillai's trace = 0.89, F(11,8) = 5.6, P < 0.05). A contrast test (compared with the last measurement at 10 AM) showed that pulse rate was significantly lower at midnight, 2, 4, 6, and 8 AM. CPAP therapy did not influence the pulse rate significantly.

There was a statistically significant decrease in mean OPP during CPAP therapy, compared to baseline (Pillai's trace = 0.25, F(1,19) = 6.4, P < 0.05; Fig. 5). A contrast test showed a statistically significant difference in OPP between the two sessions at 2, 4, 6, and 8 AM.

No correlation was found between the peak IOP or 24-hour trough-peak IOP fluctuation and the following variables: BMI, neck circumference, age, ESS, AH1, MAI, pachymetry, AH1 with CPAP, MAI with CPAP, and optimal CPAP pressure.

In a subanalysis of patients with OSA who frequently changed sleep side (left/right) at baseline and during CPAP therapy (n = 9), we found a statistically significant effect of sleep side on IOP (Pillai's trace = 0.43, F(1,8) = 5.96, P < 0.05). IOP was higher in the ipsilateral decubitus position (Fig. 6). The effect of sleep position on IOP was independent of CPAP application, since no interaction was found. No statistically significant difference in IOP between the left and right eyes was found when these nine patients were sleeping in the dorsal decubitus position.

In four patients, ocular hypertension was diagnosed with no optic disc excavation or visual field defects, and medical therapy was started. Two of them had IOPs above 25 mm Hg during the daytime and even higher IOPs at night. The other two patients had borderline IOPs during the daytime but peaked up to 32 and 33 mm Hg at night. One patient had normal-tension glaucoma with optic disc excavation and visual field defects. His baseline IOP was between 14 and 15 mm Hg, and his maximum nocturnal IOP was 20 mm Hg. Similar findings were found after CPAP was initiated.

The three subgroups of patients with OSA—ocular hypertension (OHT; n = 4), normal-tension glaucoma (NTG; n = 1), and normal OSA (n = 15)—were too small to allow valid subgroup analyses. IOP levels were higher in patients with OHT throughout the nychthemeron and regardless of CPAP treatment, compared with the NTG and normal OSA groups. The difference between the mean IOP of the OHT and normal OSA groups remained rather constant throughout the 24 hours at baseline, as well as during CPAP, and had a pattern similar to that described previously. IOP increased during CPAP, especially at night. The effect seemed to be equivalent in the OHT, the normal OSA, and the NTG groups. With regard to the mean OPP, there was no clear distinction between the three groups.

**DISCUSSION**

The circadian IOP course has been studied by many research groups. In older reports, a nocturnal IOP reduction was re-

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**TABLE 2. Maximum IOPs of 21 Patients with OSA before and during CPAP Therapy**

<table>
<thead>
<tr>
<th>Baseline Noon</th>
<th>14 PM</th>
<th>16 PM</th>
<th>18 PM</th>
<th>20 PM</th>
<th>22 PM</th>
<th>Mid-night</th>
<th>02 AM</th>
<th>04 AM</th>
<th>06 AM</th>
<th>08 AM</th>
<th>10 AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest IOP before CPAP (mm Hg)</td>
<td>32</td>
<td>28</td>
<td>29</td>
<td>28</td>
<td>33</td>
<td>25</td>
<td>27</td>
<td>26</td>
<td>27</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Patients with IOP &gt;25 before CPAP (n)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Highest IOP under CPAP (mm Hg)</td>
<td>32</td>
<td>29</td>
<td>28</td>
<td>34</td>
<td>34</td>
<td>30</td>
<td>29</td>
<td>34</td>
<td>36</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Patients with IOP &gt;25 under CPAP (n)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>
ported mainly in patients with glaucoma.17,18 However, DukeElder19 reported a nocturnal IOP elevation. In a more recent study, Liu et al.20 described a consistent circadian IOP rhythm in healthy young adults. The trough–peak difference was 3.8 ± 0.9 mm Hg, with the IOP peak occurring at the end of the sleep period.20 In a healthy aging population, he found that the trough IOP occurred at the end of the awake period, and the peak IOP appeared at the beginning of the sleep period.21 Altintaşs et al.22 reported that normal subjects did not show diurnal variation above 5 mm Hg. Nocturnal IOP increases are probably related to the supine position and the corresponding increase in episcleral venous pressure.23

As far as we know, this study represents the first analysis of the circadian IOP course in a series of patients with OSA at baseline conditions and during CPAP therapy. Baseline IOP recordings showed a significant fluctuation of IOP during the nychthemeron, with the highest values at night. The average trough–peak difference of 6.7 ± 1.5 mm Hg was higher than that found by Liu et al.20 in healthy young adults. Eighteen of the 21 patients had IOP fluctuations higher than 5 mm Hg and no patient had IOP fluctuations higher than 10 mm Hg. One month after onset of CPAP therapy, we found a significant increase in overnight IOP during CPAP application compared to baseline. The average trough–peak difference went up to 9.0 ± 2.0 mm Hg. Eighteen of the 21 patients had IOP fluctuations above 5 mm Hg and 7 had fluctuations above 10 mm Hg.

Since the highest IOPs were found at night, single IOP measurements during office hours do not permit the identification of patients who may present nychthemeral IOP spikes.24 The interaction among various physiological parameters—ocular perfusion pressure, outflow facility in sleep position, and circulating hormones while asleep—complicates the prediction of the magnitude of IOP fluctuations during overnight measurements.

The role of the IOP fluctuations in the development of glaucomatous neuropathy is controversial. One research group reported that a large fluctuation in diurnal IOP is an independent risk factor for the development or progression of glaucoma.25 Another study recently showed that the range of diurnal IOP variations was proportional to the level of IOP and concluded that diurnal variation in IOP itself was not an independent risk factor for the development of glaucoma.26 However, mean IOP was found to be a strong risk factor for the onset and progression of glaucoma.

This study not only demonstrated abnormally high 24-hour IOP fluctuations in patients with OSA treated with CPAP, compared with findings in healthy adults,20,22 but also showed a significant increase in overnight IOP during CPAP application.
compared with baseline. The pressure-raising effect of CPAP was confirmed by the significant decrease in IOP observed 30 minutes after CPAP cessation. Why CPAP therapy causes an increase in IOP is not yet understood. One could speculate that CPAP leads to an elevated intrathoracic pressure, which in turn gives a pressure elevation in the venous circulation, which may reduce the aqueous humor outflow through the episcleral veins and could explain the increase in IOP.

This hypothesis is supported by the higher IOPs values in the ipsilateral eye when patients were sleeping in the lateral decubitus position before IOP registration. The finding correlates with the assumption that venous outflow from the ipsilateral eye is decreased and on the contrary that venous outflow from the contralateral eye is increased, causing a reduction in IOP. The similarity of IOP found in both eyes of patients sleeping in the dorsal decubitus position confirms this hypothesis. Noel et al.,27 who addressed IOP changes with regard to different postural attitudes in supine patients, reported similar findings.

OSA is related to cardiovascular complications such as arterial hypertension, ischemic heart disease, heart failure, heart rhythm disturbances, cerebrovascular accidents, and pulmonary hypertension.2– 4 These cardiovascular risk factors could make patients with OSA more vulnerable to development of glaucomatous damage.

As CPAP is known to have a beneficial effect on hemodynamic parameters in patients with OSA,28 one might expect a beneficial effect of CPAP on glaucomatous progression by decreasing the risk of vascular perfusion damage. However, this study revealed a significant decrease in OPP at night during CPAP application (associated with an increase in overnight IOP) compared with baseline OPP. These results are in contrast with OPP findings in healthy subjects as reported by Liu et al.29 He found that the nocturnal OPP in the supine position was significantly higher than the diurnal OPP in the seated position.

Patients with OSA have vascular endothelial dysfunction.30 This endothelial dysfunction could reduce the ability to auto-regulate blood flow when OPP changes and may lead to unstable ocular perfusion.13 Although the effects of periodically reduced OPP on blood flow to the optic nerve head remain to be determined, it has been cautiously speculated that a reduction in OPP could lead to ischemia of the ocular tissues followed by reperfusion damage.31 A decrease in OPP could result in further glaucomatous damage in subjects predisposed to glaucomatous who are treated with CPAP.

As patients with OSA may be at higher risk of glaucomatous damage, especially those undergoing CPAP therapy, regular ophthalmic screening is necessary. Follow-up of visual field and structural changes of the optic disc will provide useful information regarding changes over time.
If glaucomatous changes or elevated IOP are discovered or develop during CPAP therapy, topical IOP lowering therapy can be started. CPAP withdrawal is not an option, due to the dramatic overall improvement of subjective sleepiness, quality of life, and cognitive functions in patients with OSA treated with CPAP.  

**Study Limitations**

We did not have a matched control group. It is difficult, however, to find obese middle-aged patients without the presence of comorbidities such as arterial hypertension, metabolic syndrome, and diabetes, which act as confounding factors and would potentially influence all measurements performed in our study. Furthermore, the number of studied patients was limited. There are no studies, however, involving assessment of ophthalmic alterations in OSA before and during CPAP therapy.

An additional weakness, common to all sleep studies, is that the patients must be awakened from sleep to check IOP. This is an inevitable drawback, but does not affect the pre- and posttreatment comparison.

**CONCLUSION**

An overnight increase in IOP is present in patients with OSA. During CPAP therapy, nocturnal IOP increases even more prominently and is paralleled by a decrease in OPP. This could be one of the factors responsible for the higher prevalence of glaucoma in this population. Whether long-term CPAP use has a deleterious influence on the development or progression of glaucoma should be investigated further. Evaluation and follow-up of the IOP, optic disc, and visual fields warrants attention in the clinical work-up of all patients with OSA, especially those treated with CPAP.

**References**


