

## Continuous 24-Hour Intraocular Pressure-Related Changes in Patients with Obstructive Sleep Apnea with and without Normotensive Glaucoma

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### Abstract

**Importance:** Obstructive apneas during sleep can affect the intraocular pressure fluctuation over 24 hours.

**Background:** Several studies found an increased prevalence of normal-tension glaucoma (NTG) in patients with obstructive sleep apneas (OSA).

**Design:** Prospective exploratory study conducted in academic setting.

**Participants:** Three patients diagnosed with OSA and 3 with OSA and NTG.

**Methods:** Ambulatory blood pressure monitoring (ABPM), overnight respiratory polygraphy and IOP-related changes monitoring in an eye by a contact lens sensor (CLS) over a 24-hour period.

**Main outcome measure:** We analyzed the effect of apneas on the CLS reading. Wake to sleep slope (W/S) and sleep to wake slope (S/W) were tested.

**Results:** An 11% increase in the mean (95% CI) overnight CLS outputs, from 185.2 (125.4-273.8) mVeq to 205.1 (192.4-219.3) mVeq, was associated with the occurrence of apneas lasted <120 s, while a 15% increase to 213.7 (194.3-235.1) mVeq occurred with apneas lasted >120 s ( $p=0.001$ ). We found no correlation between ABPM and IOP or ABPM and apneas' duration. The W/S slopes were similar between the two groups ( $P=0.41$ ), while the S/W slopes in the NTG patients differ considerably from patients without NTG ( $P=0.03$ ), with a far less steep slope in the first group.

**Conclusions and Relevance:** Obstructive apneas during sleep could affect IOP-related changes in a cumulative way. The smoother W/S and S/W slopes in NTG reveal a sort of inertia that could make some eyes more susceptible to damage following exposure to apneas.

**Keywords:** Normal-tension glaucoma; Obstructive sleep apnea; Overnight respiratory polygraphy; 24-hour intraocular pressure monitoring; Ambulatory blood pressure monitoring

### Introduction

Normal-tension glaucoma (NTG) is a form of glaucoma characterized by optic disc cupping, retinal nerve fiber layer reduction, and visual field defects in patients with intra ocular pressure (IOP) measurements constantly lower than 21 mmHg.

Known risk factors for NTG include abnormal ocular blood flow, systemic hypotension, coagulation, vascular and autoimmune disorders [1]. Progression of the optic neuropathy is generally attributed either to direct anoxic insult or to indirect changes of the optic nerve head blood flow.

Several studies found an increased prevalence of NTG in patients with obstructive sleep apnea (OSA) [2-4], a disorder characterized by recurrent complete or partial obstruction of the upper airway during sleep with repetitive pauses in breathing despite the effort to breathe [5].

This condition has been associated with an increased risk of glaucomatous optic neuropathy, either NTG or primary open angle glaucoma [6].

Several mechanisms have been suggested to explain the association between glaucoma and OSA [7]. The vascular hypothesis, assumes that the collapsing of the upper airway during sleep leads to repeated prolonged episodes of hypoxia/reperfusion, that may reduce the oxygen supply to the optic nerve, and also increase intracranial

pressure, which in turn decreases cerebral and optic nerve perfusion [6,8].

The mechanical theory proposes that obstructive apneas during sleep have the potential to raise the IOP through changes in sleep architecture with an increase of the sympathetic tone, leading to direct pressure-dependent axon damage of the optic nerve [7].

Inflammation, oxidative stress and hypercapnia have also been involved in the pathogenesis of glaucomatous damage [9].

All these mechanisms support the idea that the optic nerve damage observed in patients with OSA could be independent from a steadily elevated IOP, and might explain the increased prevalence of NTG compared to the general population, and the increased risk for glaucoma associated to severe OSA found in our previously reported cohort of 296 patients [10].

However, whether a clear link exists between OSA and glaucoma is far to be recognized [11-13]. Differences in IOP measurements depend on individuals' body circadian cycles and activities. IOP evaluation during ophthalmic visit is not enough to capture its continuous changes throughout a 24 h cycle, since more than 70% of IOP peaks occur at night or in the early morning hours [14-16]. Indeed, understanding circadian IOP pattern might help to widen our knowledge about the elusive role of IOP in NTG.

Limited data are available regarding the IOP monitoring during sleep. In healthy young volunteers, 24 h IOP fluctuations measured by Goldmann applanation tonometry (GAT) were poorly reproducible, and a single 24 h IOP assessment may not be effective enough to characterize circadian IOP fluctuations for individual subjects [17].

In patients with OSA, one study showed significant 24 h IOP fluctuations, with the highest values at night [18].

Recent technological advances have provided researchers with a device for IOP monitoring, the contact lens sensor (CLS) Triggerfish<sup>®</sup> (Sensimed AG, Lausanne, CH) design to detect IOP-related corneal curvature changes (IOP-RC) in an eye over a 24 h period [19].

Two studies applied the CLS in patients with OSA to assess modifications of the IOP-RC and possible association with apneas during sleep. Shinmei et al. showed a significant reduction of IOP-RC during apnea events in 4 out of 7 patients with moderate to severe OSA, thus assuming that obstructive apneas led to a prompt IOP reduction [20]. Jasien et al. showed the benefit of CPAP in reducing IOP-RC increase from wake to sleep transition and in rapidly decreasing of IOP-RC from sleep to wake [21].

The present study aims to assess the IOP-RC over a 24 h period and investigate the possible association between obstructive apneas and NTG comorbidity in patients with OSA.

## Methods

### Study design and population

This is a single center, prospective, exploratory, 24 h study conducted at the Eye Clinic and the Unit of Respiratory Medicine, University of Verona, according to the tenets of the Declaration of Helsinki. Institutional review board approval and written informed consent were obtained.

Patients diagnosed with OSA have been previously included in the SLEEPY study [10]. We randomly selected NTG patients among the 25

patients newly diagnosed with NTG and controls among the 63 patients without any eye morbidity in the cohort. The day of the study, patients reached the clinic early in the afternoon and returned after 24 h. Patients with NTG stopped the IOP lowering therapy 7 to 30 days before the day of the study.

We synchronized the recordings of CLS, respiratory polygraphy and BP evaluations.

### Ophthalmic examination

Diagnosis of NTG was confirmed by 30-2 SITA-Standard Humphrey visual field test (Carl Zeiss Meditec Inc., Dublin, CA) with at least two reliable visual-field examinations (fixation loss lower than 20%, false-positive rate and false-negative rate <33%). Glaucoma stage evaluation was performed using the Glaucoma Staging System 2 (GSS2) [22]. We assessed nerve fiber indicator (NFI) by optic nerve laser polarimetry (Gdx VCC, Carl Zeiss Meditec, Dublin, CA) and retinal nerve fiber layer (RNFL) thickness by optical coherence tomography (Spectralis SD-OCT, Heidelberg Engineering, Heidelberg, Germany).

Before the application of CLS, all patients underwent complete ophthalmic examinations including slit-lamp biomicroscopy of the anterior segment, fundus evaluation, best-corrected distance visual acuity (BCDVA) by the LogMAR chart, and IOP by Goldmann applanation tonometry (GAT), after topical instillation of oxibuprocain 0.4% and fluorescein 2% in sitting position. To avoid underestimation of GAT measurement, central cornea pachimetry was verified by Visante OCT (Carl Zeiss, Oberkochen, Germany).

The CLS was placed at the end of the visit on day 1 and 15 min after the CLS removal following 24 h monitoring, patients repeated slit lamp examination and GAT.

### IOP-related changes recording with the contact lens sensor (CLS)

The disposable CLS (Sensimed Triggerfish<sup>®</sup>, Lausanne, CH) was applied to the eye with the worse glaucomatous damage or to the right eye in the control patients, selecting the appropriate CLS size based on keratometric measures assessed by optical biometry (Lenstar LS900, Haag-Streit, Koeniz, CH) among the three available (steep, medium or flat).

The CLS records corneal curvature changes (expressed in mVeq) every 5 min for the duration of 30 sec, giving 288 measurements over a 24 h period.

The portable recorder, containing the battery that powers the device, was worn around the patients' waist and the device switched on. Patients were suggested to instill lubricating eye drops every 2 h in the eye with CLS during daytime.

### Respiratory polygraphy

The overnight respiratory polygraphy at home consists in continuously recordings from 11:00 pm to 7:00 am of oro-nasal flow, thoracic-abdominal motion, pulse oximetry, cardiac frequency and body position.

Two abdomen and thorax sensor belts were applied to patient and the portable recorder (Embletta-PSD Somnologica, Sapiolife, Reykjavik, IC) hang to the abdominal belt. A disposable pulse oxymeter connected to the device was stuck to the right first finger and

nasal cannulae were plugged in the device and placed in a pocket, ready to be put on by the patient before going to bed. The recorder turns on at 11:00 pm and switches off at 7:00 am automatically.

We advise patients to maintain their usual daily activity and any current systemic therapy, if any, except showering or swimming, and continuous positive airway pressure (CPAP).

Initiating of sleeping time was considered when less than 3 blink-like spikes were detected on a 30 seconds interval of CLS recording. The sleep period then continued until the number of blink-like spikes returned to be consistently above 3 in a 30 sec interval. We used the patients' logbook on which patients reported the time they went to sleep and woke up to calculate the W/S and the S/W slopes of CLS measurements and to assess the percentage of dipping in BP as described below.

The RP recordings were downloaded on a computer and scored. The number of apnea episodes (complete cessation of airflow for 10 sec or greater) and of hypopnea episodes (reduction in airflow >50% for 10 sec or greater with a decrease of oxygen saturation of >3%) per hour of sleep (AHI) was used to determine the severity of OSA according to standard criteria [23].

### Ambulatory blood pressure monitoring (ABPM)

ABPM was recorded automatically (Ambulatory Blood Pressure-Space Labs model 90217, Spacelabs Healthcare, Verona, IT) every 15 min during the day and every 20 min during the night. Cuff sizes (20-31 cm or 28-36 cm) were placed according to the left arm circumferences measured at the biceps level. Data from ABPM included systolic pressure (SP), diastolic pressure (DP), mean artery

pressure (MAP), pulse pressure (PP), heart frequency (HR). Accordingly to the American Heart Association (AHA), we calculate the reduction (%) of the systolic BP during the night compared to daytime (dipping) and classified patients as nondipper (<10%), dipper (from 10% to 20%) or extreme dipper (>20%).

### Statistical methods

We calculate the W/S and S/W slope of CLS measurements by fitting linear regression to measurements from 1 h before transition from W/S or S/W to 1 h after.

To highlight the potential association between OSA and CLS changes, we summed the duration of apnea events occurring during the 5 min preceding the CLS measurement.

We used the ANOVA test to compare W/S and S/W slopes in NTG and non-NTG patients. The database was examined as longitudinal data. We further investigated the relationship between IOP-RC vs. apneas and MAP vs. apneas with generalized estimating equations model with distribution family gaussian, log link function, and correlation structure exchangeable [24]. Regression models were carried out by means of the xtgee function of the statistical package Stata V.13 statistical software (Stata Corporation, Stata Statistical Software: Release 13.0. College Station, TX). The P value was set at 0.05 and confidence intervals calculated at 95%.

### Results

Six Caucasian male were enrolled (Table 1). All showed reliable tracks from the three devices.

No.	Age, yrs	BMI, kg/m <sup>2</sup>	NFI	RNFL				MD	PSD	GSS2	IOP, mmHg	BCDVA, LogMar
				Nasal	Superior	Inferior	Temporal					
1	48	44.1	52	66	90	54	46	-12.88	-1.22	S3	16	1
2	66	30.1	53	51	75	58	52	-0.23	11.34	S3	17	1
3	57	28.4	33	53	90	75	55	-2.71	5.51	S2	11	1.8
4	66	29.4	29	79	96	127	59	-0.06	2.3	S0	16	0.8
5	55	28.9	17	84	106	127	51	-0.56	2.56	S0	14	1
6	46	25.2	21	77	118	132	47	-0.87	1.58	S0	12	1

**Table 1:** Demographics and clinical characteristics.

Patient no. 6 was currently smoker and no. 2 was ex-smoker. Patient no. 1 and no. 6 were on CPAP therapy and discontinued CPAP the night of the study. Patient no. 4 reported type 2 diabetes mellitus. None of the patients reported medical history of arterial hypertension.

NTG patients showed ophthalmoscopic signs of glaucomatous optic neuropathy accompanied by NFI >30 in at least one eye without signs of secondary glaucoma (pseudoexfoliation and pigment dispersion syndrome) after pupil dilation. Visual function test showed defects

consistent with glaucoma (nasal step, paracentral or arcuate scotomas or arcuate blind spot enlargement) with a PSD >5% and Glaucoma Hemifield test outside normal limits and at least three contiguous points on the total deviation probability plot at the <2% level. Patients without NTG showed healthy eyes either ophthalmoscopic or functionally.

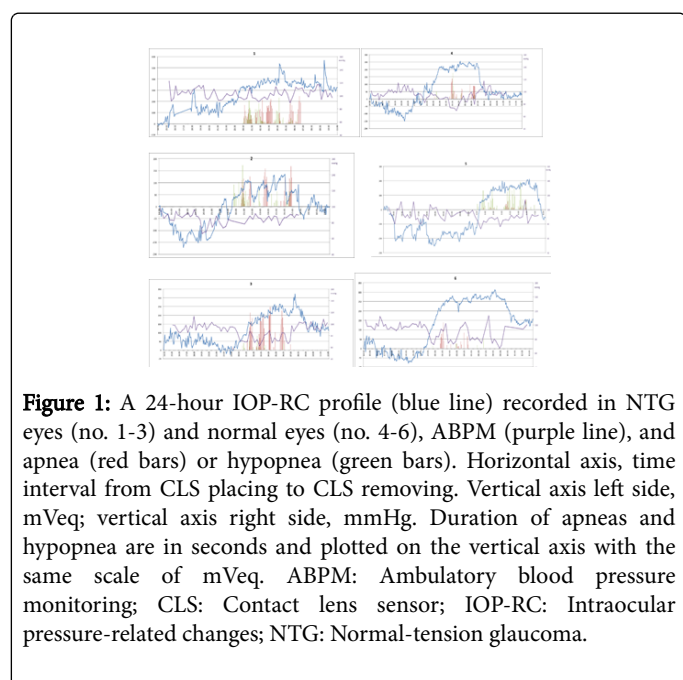
Results of RP, ABPM, and CLS for each patient are reported in Table 2.

Patient	AHI, events/h	ODI, events/h	Mean SpO <sub>2</sub> , %	Lowest SpO <sub>2</sub> , %	MAP (mean ± SD), mmHg	HR (mean ± SD), mmHg	Sistolic dipping %
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					Sleep hours	Wake hours	Sleep hours	Wake hours	
1	53.5	50.4	94.8	83	101.4 ± 7.8	103.93 ± 7.84	73.25 ± 7.51	85.5 ± 12.6	5.2
2	22.3	19.1	94.9	88	84.8 ± 3.7	85.4 ± 8.7	59.4 ± 4.7	74.8 ± 9.3	0.9
3	22.9	20.7	96.2	87	76.2 ± 8.9	96.0 ± 6.0	53.4 ± 2.8	69.7 ± 9.8	15.3
4	13.1	7.4	97.5	88	88.3 ± 8.6	98.6 ± 6.6	62.9 ± 3.7	70.2 ± 6.4	9.6
5	22.5	25.1	93.9	86	87.3 ± 7.8	93.9 ± 7.6	62.5 ± 3.3	76.2 ± 8.3	4.7
6	6.4	1.3	95.8	92	84.6 ± 11.7	98.5 ± 4.6	68.9 ± 9.1	78.8 ± 8.6	10.9

**Table 2:** AHI: apnea-hypopnea index; ODI: oxygen desaturation index; MAP: mean artery pressure; HR: heart rate; SpO<sub>2</sub>: Oxygen saturation from pulse oxymetry.

Measurements of RP, CLS, and MAP plotted together are reported in Figure 1.



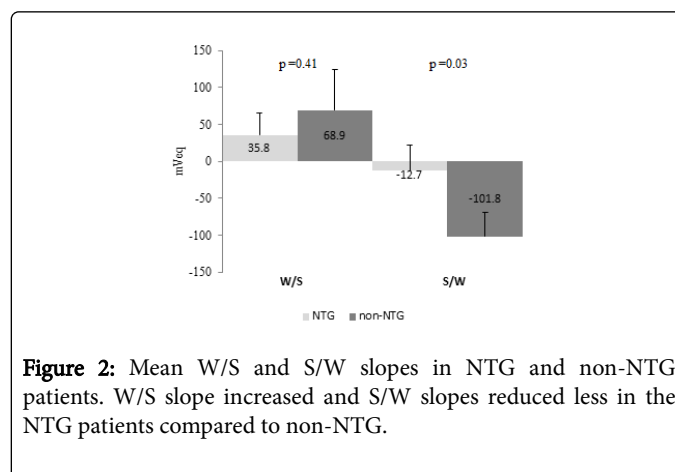
**Figure 1:** A 24-hour IOP-RC profile (blue line) recorded in NTG eyes (no. 1-3) and normal eyes (no. 4-6), ABPM (purple line), and apnea (red bars) or hypopnea (green bars). Horizontal axis, time interval from CLS placing to CLS removing. Vertical axis left side, mVeq; vertical axis right side, mmHg. Duration of apneas and hypopnea are in seconds and plotted on the vertical axis with the same scale of mVeq. ABPM: Ambulatory blood pressure monitoring; CLS: Contact lens sensor; IOP-RC: Intraocular pressure-related changes; NTG: Normal-tension glaucoma.

One patient with NTG (no. 3) and one among the controls (no. 6) were classified as dippers since nocturnal systolic BP reduced of 15.3% and 10.9%, respectively.

Considering all patients in the analysis, the mean (95% CI) CLS value during sleep was 185.3 (125.4 to 273.8) mVeq. Equation model analyses showed that the occurrence of apneas with an overall duration <120 s was associated to a rise in mean (95% CI) overnight CLS outputs to 205.1 (192.4 to 219.3) mVeq (11% increasing) while an overall duration >120 s raised the CLS output to 213.7 (194.3 to 235.1) mVeq (15% increasing) (P=0.001).

We found no differences between MAP and CLS measurements or MAP and the duration of apneas.

Results of the W/S and S/W slopes analyses are shown in Figure 2.



**Figure 2:** Mean W/S and S/W slopes in NTG and non-NTG patients. W/S slope increased and S/W slopes reduced less in the NTG patients compared to non-NTG.

## Discussion

This study evaluates simultaneously IOP-RC assessed with CLS, duration of obstructive apneas, and fluctuation of blood pressure in patients with OSA and NTG or healthy eyes.

In patients with glaucoma, IOP elevation and peaks may occur during the night and peaks are the best predictor of glaucoma progression [25]. The cause of nocturnal IOP elevation is multifactorial. One important cause is supine and lateral positions [26]. Mansouri et al. confirmed in healthy volunteers that the increase of IOP (by using the CLS) happens following body position changing from sitting to supine due to the relative position of the eye to the heart [27].

Pajic et al. observed that in patients with NTG the curves from CLS correspond to those in healthy patients [28], and confirmed the presence of the nyctohemeral rhythm of IOP found by Renard et al. [29].

Our results are consistent with these findings, and all the circadian IOP-RC from CLS curves showed an increase during the sleep and a decrease at wakeup and during the daytime.

Although the significant association of OSA and NTG [10,12], the pathophysiological mechanisms that underlie this association are unknown. Shinmei et al. found that in healthy subjects with OSA during the night, the CLS curve declines immediately throughout an obstructive apnea event [20]. Authors postulate that the airways

collapse during an obstructive apnea produces a negative intrathoracic pressure, due to the effort to inspire, causing a decrease in IOP-RC.

On the contrary, we found a positive correlation between apneas and CLS measurements, a result not comparable with that of Shinmei because we considered the length of apnea episodes occurred in the 5 min before the CLS recording instead of the variation in mVeq occurred exactly during apnea episodes.

We are confident that our approach can better represent the real pathophysiological events that occur during sleep and affect patients with OSA. In fact, during an obstructive apnea, subjects exert efforts to breathe, either inspiring or expiring so both Mueller and Valsalva maneuvers are present. The raise in venous pressure during the Valsalva component of apneas associated with the sympathetic over-activation detected in patients with OSA may contribute to an overall raise in the pressure of the ocular venous drainage system [30], thus explaining the correlation we found between the duration of apneas and the raise in CLS parameter. The sympathetic over-activation during apneas may lead also to an increase in basal extraocular muscular tone, which in turn may induce an increase in IOP.

According to our study, the S/W slope is significantly flatter but also the increase in the W/S slope is less prominent in glaucomatous patients. It is conceivable that NTG patients show a sort of inertia in response to physiological variations compared to non-NTG, fact that could make these patients' eyes more prone to have a damage following the persistent exposure to apneas.

In a prospective exploratory study on 4 vs. 4 POAG and non-POAG patients evaluated with CLS, Jasien et al. found that CPAP therapy reduced the increase in W/S slope in POAG patients and augmented the increase in non-POAG patients. On the contrary, the effect on S/W slope was in the direction of a decrease in both groups, more evident in the POAG group. These findings, even though on a different population, support the hypothesis that in glaucomatous patients there may be a sort of inertia in the structural system of the eye [21].

Autoregulatory disorder of the blood flow mechanism in the optic nerve head is a further important known risk factor for the development of glaucoma [31].

Previous studies have shown that patients with NTG and POAG have low BP levels at night [32]. Leske et al. [33] reported that low BP levels might increase the progression of POAG and NTG. On the contrary, Kocatürk et al. found that only NTG patients had low BP levels while POAG patients had higher BP levels than did the controls [34].

None of our patient had a diagnosis of arterial hypertension even though OSA is a known risk factor for hypertension, and 2 patients showed a dipper profile. Yorgun et al. [35], investigating the short-term effects of CPAP treatment on BP and nondipper or dipper status in patients with OSA without a prior diagnosis of hypertension, found that nondipping phenomenon was a common condition among patients with OSA even in normotensive patients which recovered after CPAP treatment. The authors postulated that the sympathetic nervous system over-activation in patients with OSA causes nondipping phenomenon, a possible early sign of hypertension development.

The exploratory nature of this study cannot allow generalizing any conclusion. The reproducibility and validity in the estimation of IOP by CLS remains unknown [36], although Liu et al. [37] reported that

the 24 h peak timing obtained with the CLS was statistically similar to the 24 h IOP peak timing obtained with the pneuma-tonometer. Moreover, De Moraes et al. [38] stated that a direct association between the CLS output and GAT is not recommended, because the former provides values based on electric signals (mVeq) that, despite being related with the latter, does not measure the same phenomenon. However, they postulate that CLS parameters, which are derived from changes in volume and elasticity from ocular tissues, could provide indirect information regarding IOP-driven stress within the connective tissues of the optic nerve head that ultimately result in glaucomatous changes.

In conclusion, IOP in NTG needs to be examined thoroughly to shed ever more light on its implication in the onset and pathogenesis of NTG in OSA. Data from our study are not conclusive, although may pave the way for a further investigation into the elusive relationship between OSA and NTG.

However, our results suggest considering the occurrence of OSA in patients with NTG not only as a simple comorbidity but rather as a pivotal issue that could reflect a possible causative factor of the ocular pathology.

## Conflict of Interest

The authors declare that they have no competing/conflict of interests.

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