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Continuous Intraocular Pressure Monitoring During Nocturnal Sleep in Patients With Obstructive Sleep Apnea Syndrome

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PURPOSE. To evaluate intraocular pressure (IOP) changes during nocturnal sleep in patients with obstructive sleep apnea syndrome (OSAS) using a contact lens sensor (CLS).

METHODS. This was a prospective cohort study. Seven OSAS patients who had no ocular diseases except mild cataract were enrolled. Each subject underwent CLS-based continuous IOP monitoring on one eye simultaneously with overnight polysomnography. We classified the nocturnal IOP records into nonapnea IOP and apnea IOP, according to the duration of apnea events on polysomnography within each IOP measurement time of 30 seconds every 5 minutes.

RESULTS. Differences between IOP levels during nonapnea and apnea phases were statistically analyzed. The mean apnea-hypopnea index, the total number of these events per hour of sleep, was 44.2 ± 21.0 , indicating the participants' severity of OSAS as moderate to severe. The mean range of IOP fluctuations during nocturnal sleep was 262.3 ± 59.5 mmHg. All patients showed lower mean IOP levels during apnea events than during nonapnea phases, with statistically significant differences detected in four of the seven patients. On average, in all seven eyes, IOP values significantly decreased by 23.1 ± 16.4 mmHg in association with apnea events.

CONCLUSIONS. Obstructive apnea led to an immediate IOP decline during nocturnal sleep in patients with OSAS. Attention should be paid to IOP-independent etiology, such as episodic hypoxia, potentially linking OSAS and glaucoma.

Keywords: obstructive sleep apnea syndrome, intraocular pressure, glaucoma, contact lens sensor, episodic hypoxia, nocturnal sleep

Obstructive sleep apnea syndrome (OSAS) is characterized by snoring, excessive daytime sleepiness, and insomnia. Epidemiologic studies revealed a prevalence of 2% to 20% and a background etiology including obesity, male sex, upper respiratory tract abnormality, consumption of alcohol, snoring, and thick neck.^{1–3} Recent data suggest that OSAS may be associated with a number of cardioneurovascular risk factors, such as hypertension,^{4,5} insulin resistance, impaired glucose tolerance,^{6,7} and dyslipidemia.^{8,9} Untreated OSAS has previously been reported as the cause of the highest incidence of ischemic stroke.^{10,11} Moreover, OSAS has been shown to link to various ocular disorders including floppy eyelid syndrome, keratoconus, nonarteritic anterior ischemic optic neuropathy, papilledema secondary to increased intracranial pressure, and glaucoma.^{12–23}

Glaucoma, the leading cause of irreversible blindness worldwide, is an optic neuropathy with characteristic alterations of an optic disc appearance corresponding to visual field disturbances.²⁴ Most of these abnormalities are related to the elevation of intraocular pressure (IOP) causing damage to the optic nerve head directly.²⁵ However, given that at least some glaucoma patients have a normal or relatively low IOP range,

other systemic conditions, such as diabetes, cardiovascular disease, and obesity, may also be relevant.^{26,27}

Numerous previous studies have described the involvement of primary open-angle glaucoma and normal-tension glaucoma in patients with OSAS.^{18–23} Karakucuk et al.²⁰ indicated a positive correlation between IOP levels and the severity of OSAS. Moghimi et al.²³ reported that OSAS patients also had worse visual field indices and lower nerve fiber layer parameters than age-, sex-, and body mass index (BMI)-matched controls. Ferrandez et al.²⁸ reported that patients with OSAS exhibited reduced retinal sensitivity compared with healthy controls, although IOP was lower in OSAS patients. These findings suggest that the relationship between OSAS and glaucoma remains incompletely understood, especially with regard to an IOP change.

Intraocular pressure is a dynamic parameter with a circadian rhythm and is affected by sleep structure.²⁹ Studies with 24-hour IOP monitoring found that approximately two-thirds of glaucoma patients had their highest IOP levels outside regular clinic hours, most frequently during the nocturnal sleep period.^{30,31} Until recently, however, nocturnal IOP measurements have been based on the conventional methods (e.g.,



TABLE 1. Characteristics of Patients With OSAS

Patient	Sex	Age, y	BMI, kg/m ²	Apnea, per Night	Hypopnea, per Night	AHI, per Hour	Mean SpO ₂ , %	Min SpO ₂ , %
1	Male	59	38.2	69	130	22.5	95.4	82.0
2	Male	67	26.1	11	222	32.1	96.8	79.0
3	Male	44	26.7	301	385	46.1	97.6	83.0
4	Male	50	27.4	384	470	55.4	95.7	75.0
5	Male	52	29.5	175	405	52.9	96.8	82.0
6	Male	49	35.3	226	694	79.9	91.2	65.0
7	Male	43	35.0	70	154	20.5	94.4	68.0

Mean SpO₂, mean value of oxygen saturation; Min SpO₂, minimum value of oxygen saturation.

Goldmann applanation tonometry) repeatedly applied under awakening conditions in the night. A major breakthrough was made when Leonardi et al.^{32,33} updated the concept of a soft contact lens with an embedded wireless sensor and developed an approved commercial product. The contact lens sensor (CLS) is a recently established device allowing 24-hour continuous IOP monitoring with no requirement of waking subjects up during the nocturnal sleep period.^{34–39} We herein report the first evidence that shows the impact of apnea-hypopnea events on IOP values evaluated with overnight continuous monitoring using the CLS device in patients with OSAS.

METHODS

Subjects

Twenty-five patients diagnosed with OSAS in our Sleep Clinic at KKR Sapporo Medical Center were nominated between May 2013 and January 2014. Before enrollment in this study, these OSAS patients underwent routine ophthalmic examinations to rule out any ocular abnormalities that would possibly affect IOP monitoring. As a result, six patients with myopia more than 4 diopters, two patients with normal-tension glaucoma requiring antiglaucoma treatments, and two patients with other diseases (diabetic retinopathy and panic disorder) were excluded from the study. Of the remaining 15 candidates, 8 patients did not give informed consent to enrollment. Eventually, seven male patients whose mean age was 52 ± 8.5 years (range, 43–67) agreed to participate in this study (Table 1). All the participants showed IOP of less than 22 mm Hg via iCare rebound tonometry (Tiolat Oy, Helsinki, Finland), normal ganglion cell complex map on RS-3000 optical coherence tomography (NIDEK, Gamagori, Japan), and refractory errors between ±3 diopters. No participants had any history of eye diseases except mild cataract or previous ocular surgeries. Informed consent was obtained from all seven subjects after explanation of the nature and possible consequences of the study. Our institutional review boards (Hokkaido University Hospital and KKR Sapporo Medical Center) prospectively approved the project, which adhered to the tenets of the Declaration of Helsinki. The registration number for this prospective study in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) is UMIN000017950.

Continuous IOP Monitoring

The enrollees were admitted to KKR Sapporo Medical Center overnight for continuous IOP monitoring using the SENSIMED Triggerfish CLS (Sensimed AG, Lausanne, Switzerland) as previously described.^{34–39} In brief, the wireless CLS device was attached to one randomly selected eye of each subject, and

an orbital patch containing a loop antenna was applied and connected to a portable recorder overnight. The CLS system is capable of recording a measurement every 5 minutes for a duration of 30 seconds, giving a total of 288 measurements over a 24-hour period. One average value of IOP fluctuating for 30 seconds can be obtained in each measurement. In this session, approximately 144 measurements were repeated for each patient overnight. Data from the sensor were transmitted wirelessly to the loop antenna in the soft patch worn around the eye and subsequently to the portable recorder. At the end of the recording, data from the portable recorder were transferred to a computer containing the software for analysis of the signals. Recorded overnight profiles were visualized graphically across a computer interface. The recording unit was expressed in mV eq, reflecting changes in the curvature of the cornea.

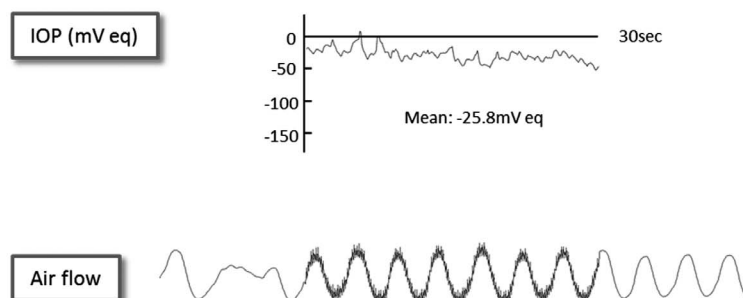
Polysomnography

The participants underwent Sandman Elite polysomnography (Version 7.2; Embla Systems LLC, Ottawa, Canada) concurrently with overnight IOP monitoring. Data from the polysomnography devices (electroencephalogram, chin and anterior tibial electromyogram, electrocardiogram, airflow using nasal pressure and oronasal thermistor, respiratory excursions using inductance plethysmography, and pulse oximetry) were analyzed by experienced sleep medicine technologists naïve to the aim of this study on nocturnal IOP monitoring. Respiratory events were scored blindly using the 2007 AASM (American Academy of Sleep Medicine) alternative criteria, in which apnea was defined as the absence of airflow lasting >10 seconds, with hypopnea as a >50% reduction in airflow from the baseline value lasting >10 seconds and associated with a 3% oxygen desaturation or arousal. The apnea-hypopnea index (AHI), an index used to represent the severity of OSAS, was defined as the total number of apnea and hypopnea events per hour of sleep.

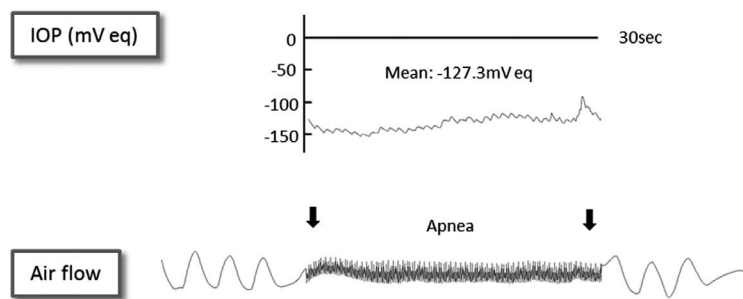
Classification of IOP Records

To investigate the influence of apnea-hypopnea events on IOP values, we classified all the nocturnal IOP records according to the duration of these events within each 30-second measurement via the CLS (Fig. 1). Nonapnea IOP was defined as a mean value of each IOP measurement averaged for 30 seconds during which neither apnea or hypopnea occurred (Fig. 1A), while apnea IOP was defined as a mean value of each IOP measurement with apnea and/or hypopnea lasting over 20 of 30 seconds (Fig. 1B). This threshold of 20 seconds was determined at our discretion to obtain a sufficient number of records for statistical comparison, as apnea events lasting up to 30 seconds were rarely observed in our case series. The remaining IOP records were excluded from the analyses because those measurements were interrupted by awakening,

A. Non-apnea IOP



B. Apnea IOP



C. Excluded IOP

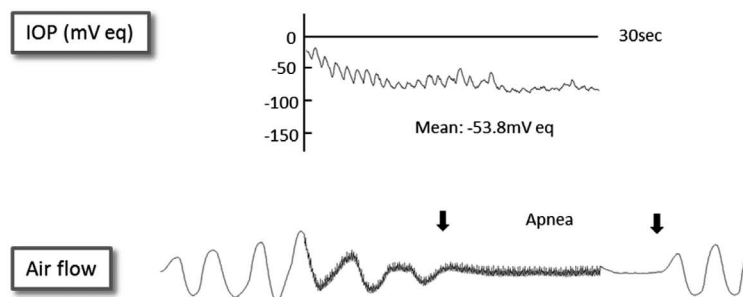


FIGURE 1. Classification of IOP records. Nocturnal IOP records classified according to the duration of apnea events within each 30-second measurement of IOP. (A) Nonapnea IOP defined as the mean value of an IOP measurement with no apnea involved. (B) Apnea IOP defined as the mean value of an IOP measurement with apnea lasting over 20 of 30 seconds. (C) Excluded IOP due to an IOP measurement not so predominantly (i.e., 20 seconds or less) involved with apnea.

or not so predominantly (i.e., 20 seconds or less) involved with either of the respiratory events (Fig. 1C).

Statistical Analyses

All results were expressed as the mean $\pm$ standard deviation (SD). Differences between nonapnea IOP and apnea IOP were analyzed using Student's *t*-test for each of the seven participants. For all tests, *P* values < 0.05 were considered statistically significant.

RESULTS

Severity of OSAS

Table 1 shows patients' characteristics related to the severity of OSAS. All the enrollees were overweight (BMI > 25), with a mean BMI of 31.2 ± 4.9 kg/m². The mean number of apnea

and hypopnea events overnight was 176.6 ± 136.2 and 351.4 ± 200.1 , respectively. Their mean AHI was 44.2 ± 21.0 , ranging from 20.5 to 79.9. Of the seven participants, five had severe AHI (>30) and two had moderate AHI (15–30). Of all the apnea events recorded, only 1.3% showed central apnea, in which the brain temporarily stops sending signals to the muscles that control breathing, indicating that most of the apnea events observed in the current study were obstructive. The mean oxygen saturation and the minimum oxygen saturation were $95.4 \pm 2.1\%$ and $76.3 \pm 7.3\%$, respectively, showing the frequent occurrence of episodic hypoxia during nocturnal sleep in our OSAS patients.

Overnight IOP Fluctuations

Overnight IOP fluctuations were recorded together with apnea and hypopnea occurrences from the seven participants with OSAS (Fig. 2). These respiratory events during nocturnal sleep

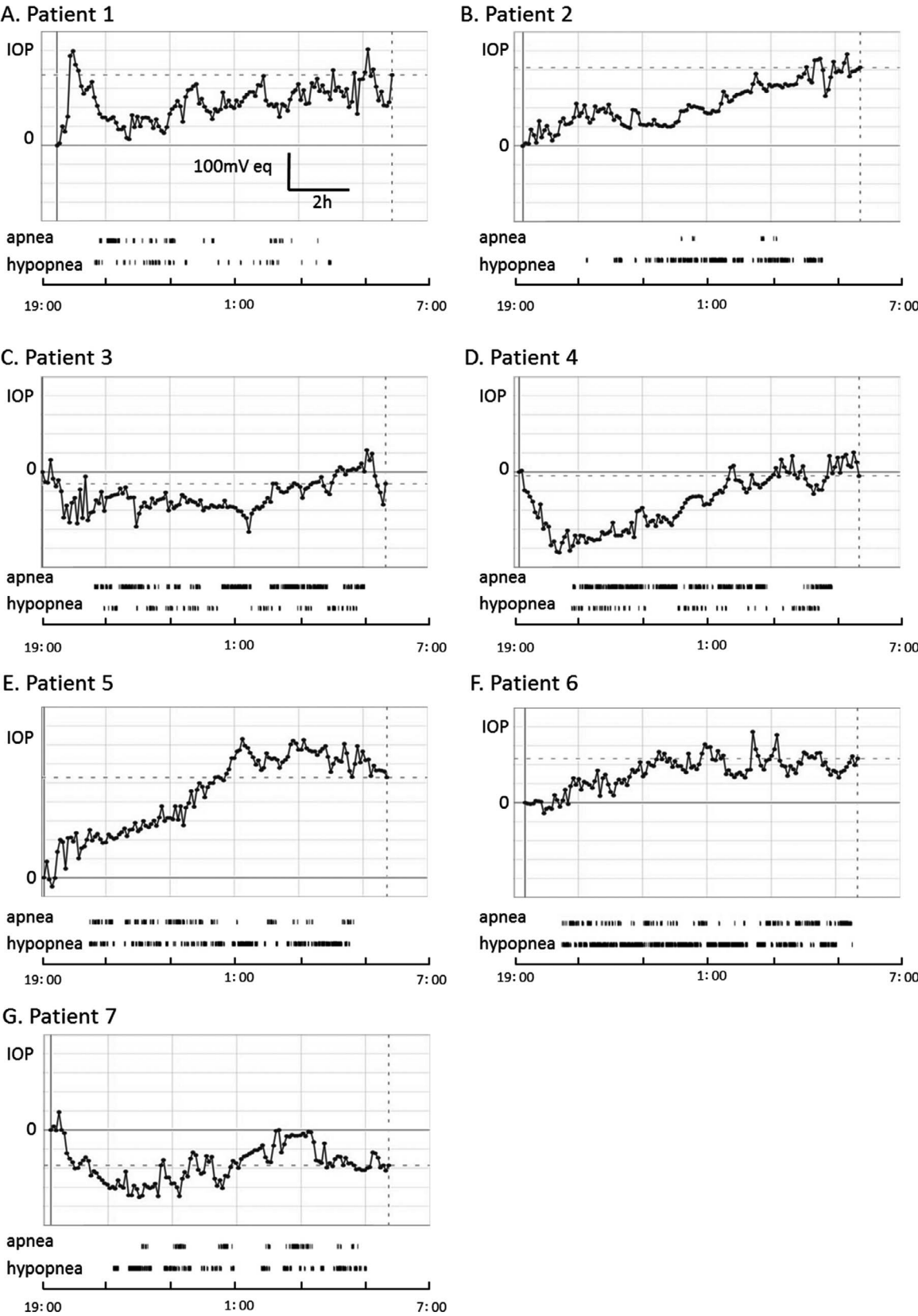


FIGURE 2. Overnight IOP fluctuations. Overnight IOP fluctuations recorded together with apnea and hypopnea occurrences shown in *dots* under each IOP. (A–G) Overnight IOP curves and respiratory events obtained from patients 1 through 7. Respiratory events showing apparently no regular pattern in each patient. The overall nocturnal curves seemingly masking the immediate impact of apnea on IOP reduction (Table 2), due to the much smaller degree of apnea-induced changes compared to the mean overnight variations (23.1 vs. 262.3 mV eq).

TABLE 2. Differences in CLS-Based IOP Levels Between Nonapnea and Apnea

Patient	Nonapnea		Apnea		Difference of IOP, mV eq	P Value
	Number of Records	IOP, mV eq	Number of Records	IOP, mV eq		
1	86	117.9 ± 40.7	8	88.9 ± 27.5	29.0	0.0260*
2	69	133.7 ± 57.5	14	117.8 ± 39.7	15.9	0.1638
3	69	−52.0 ± 45.2	32	−68.3 ± 27.9	16.3	0.0349*
4	34	−48.0 ± 71.0	55	−101.5 ± 57.9	53.5	0.0001†
5	48	238.3 ± 101.1	26	209.2 ± 84.4	29.1	0.1076
6	34	98.0 ± 38.0	37	81.0 ± 34.1	16.9	0.0260*
7	70	−89.5 ± 37.1	18	−90.8 ± 64.2	1.3	0.4541

* $p < 0.05$, Student's *t*-test.† $p < 0.01$, Student's *t*-test.

are shown in dots under each IOP. The first measurement of the IOP recording session, just after activation of the CLS device, was arbitrarily set at 0 mV eq. The subsequent measurements represented relative signal changes. The mean difference between maximum and minimum values in overnight IOP fluctuations was 262.3 ± 59.5 mV eq, ranging from 214.2 mV eq (patient 3) to 388.2 mV eq (patient 5). The currently observed variations of CLS-based IOP values were comparable with regard to a circadian rhythm to those recently shown in normal subjects,^{34,35} whereas these respiratory events demonstrated apparently no regular pattern and seemingly no correlation with the overnight IOP curve in each patient.

Impact of Apnea on IOP

To examine the immediate response to IOP dynamics via each of the overnight respiratory events, we statistically compared differences between nonapnea IOP (Fig. 1A) and apnea IOP (Fig. 1B) levels for each of the seven participants (Table 2). Importantly, mean values of apnea IOP were lower than those of nonapnea IOP in all subjects, with statistically significant differences detected in four (patients 1, 3, 4, 6) of seven OSAS patients. On average, of the seven eyes examined, IOP values significantly ($P = 7.6E-6$; Student's *t*-test) decreased by 23.1 ± 16.4 mV eq in relation to events. This direct impact of obstructive apnea on IOP reduction appeared to be masked by the overall nocturnal curve (Fig. 2), because the degree of apnea-induced change was approximately 11 times smaller than the entirety of overnight variations (23.1 vs. 262.3 mV eq).

DISCUSSION

The present study demonstrated, for the first time to our knowledge, overnight IOP fluctuations during nocturnal sleep in patients with moderate to severe OSAS. The CLS-based continuous IOP monitoring revealed that IOP levels significantly declined in immediate response to apnea events, suggesting an elusive link between OSAS and glaucoma in terms of how OSAS contributes to the pathogenesis of glaucoma as a proposed risk factor.^{18–23}

The currently used CLS device is based on a novel approach, in which changes in corneal curvature and circumference are assumed to correspond to changes in IOP.^{32,33} Although this device, whose value is expressed in mV eq, cannot estimate the absolute value of IOP in mm Hg, the relationship between changes in these two parameters has been validated in preliminary ex vivo experiments with porcine eyes,^{32,33} and in clinical trials with healthy volunteers.^{34,35} The present study demonstrated overnight IOP fluctuations similar to those shown in these recent reports,

suggesting that the IOP variations in OSAS patients are governed at least in part by a circadian rhythm, while apnea and hypopnea events randomly and frequently occurred during sleep, which appeared to be independent of the overall nocturnal IOP curve.

We hypothesized that frequent occurrence of obstructive apnea during the night would have some impact on nocturnal IOP dynamics in terms of breath holding, leading to a mechanistic insight into the pathogenesis of OSAS-associated glaucoma.^{18–23} Vieira et al.⁴⁰ reported that IOP increased significantly during a bench press exercise and that breath holding during the exercise led to a greater IOP increase. The elevation of IOP was theorized to result from the Valsalva maneuver,⁴¹ which, in association with contraction of abdominal and thoracic muscles, caused an extra increase in intrathoracic venous pressure and subsequent compression of the intrathoracic venous system.⁴²

In stark contrast to the Valsalva maneuver, apnea events significantly reduced the average IOP levels in the present study. This result may in fact be complementary to the principle of the Valsalva maneuver. At the time of obstructive apnea, OSAS patients allow their airways to collapse at inspiration, producing negative intrathoracic pressure (Fig. 3A), while in contrast, breath holding at expiration during exercise (i.e., the Valsalva maneuver) results in positive intrathoracic pressure (Fig. 3B). This opposite direction of intrathoracic pressure is speculated to contrast obstructive apnea and the Valsalva maneuver with regard to the distinctly different regulation of IOP changes.

Our current observation and speculation may also be supported by a previous study showing a significant decrease in IOP due to forced inspiratory effort against a closed airway,⁴³ also known as the Muller maneuver, which corresponds to the reverse of the Valsalva maneuver. Although the Muller maneuver was applied to young healthy volunteers while completely awake, this previous and our present studies confirmed the theoretical basis indicating that negative intrathoracic pressure, even if generated while awake or asleep, would cause an immediate IOP-lowering response. Moreover, Pepin et al.⁴⁴ reported that treatment with continuous positive airway pressure for patients with severe OSAS led to a significant increase in nocturnal IOP. Our observational data, in concert with this interventional study, reinforced the concept of tight correlation between intrathoracic pressure and IOP, especially in OSAS patients under sleeping conditions.

A major limitation to our study is the relatively small sample size; thus no comparison was made depending on the severity of OSAS. In the current CLS system, the unit of mV eq cannot be converted to the conventional pressure values in mm Hg, and the IOP values averaged for 30 seconds can be obtained

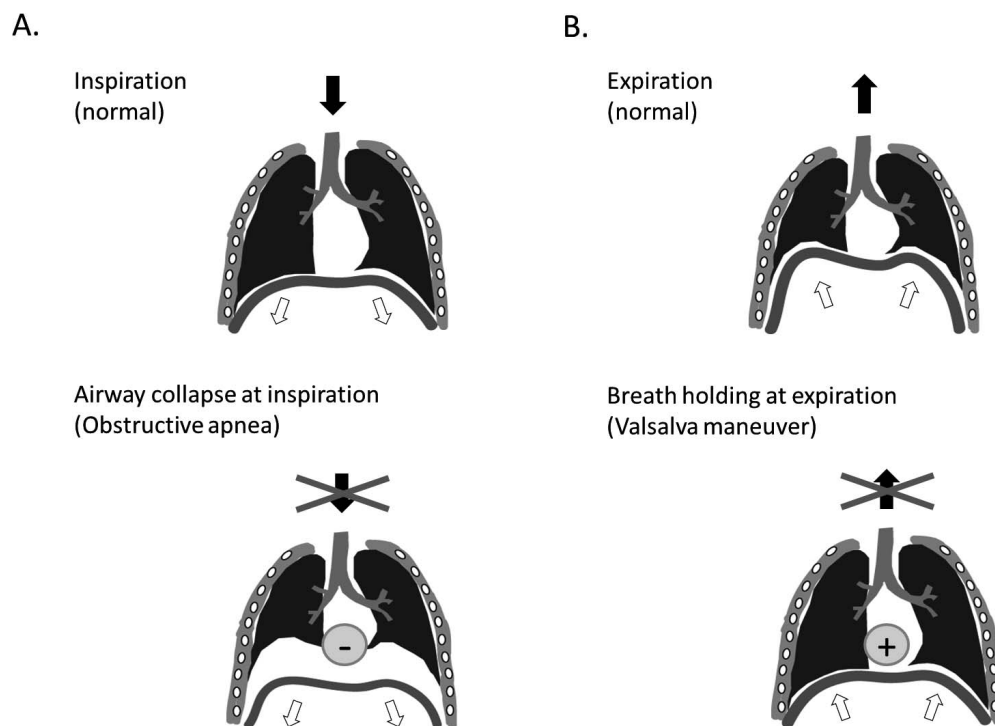


FIGURE 3. Intrathoracic pressure changes in obstructive apnea and the Valsalva maneuver. Schematic drawings showing the opposite regulation of intrathoracic pressure changes in obstructive apnea and the Valsalva maneuver. (A) Normal inspiration (*top*) and obstructive apnea (*bottom*). Airway collapse at inspiration generating negative intrathoracic pressure, as seen during sleep in OSAS patients. (B) Normal expiration (*top*) and the Valsalva maneuver (*bottom*). Breath holding at expiration generating positive intrathoracic pressure, as seen during physical exercise.

only partially (i.e., 1/10 of every 5 minutes) during the entire measurement time. The definition of apnea IOP, first introduced at our discretion to fix the threshold of 20 seconds, has not been used elsewhere.

Nevertheless, this study is the first to show the acute IOP-lowering effect of apnea-hypopnea events in OSAS patients under sleeping conditions via overnight continuous monitoring. Attention should be paid to various IOP-independent factors potentially linking OSAS and glaucoma, including ocular perfusion pressure, autonomic dysfunction, ischemia, inflammation, oxidative stress, mitochondrial dysfunction, and hypercapnia, all of which stem from episodic hypoxia during nocturnal sleep in OSAS patients.⁴⁵ Future and further studies are required to better understand the mechanism of OSAS-associated glaucoma leading to retinal ganglion cell death without IOP elevation.

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