

# Alterations on Microcirculation of Optic Nerve Head Before and After OSA Surgery

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**Objective:** Obstructive sleep apnea/hypopnea syndrome (OSA) can compromise oxygenation of the optic nerve and cause glaucomatous optic neuropathy; however, there were no studies to investigate the changes of optic nerve microcirculation in patients with OSA before and after treatment. We conducted the first study to assess whether OSA surgery will change the optic nerve microcirculation in patients with OSA.

**Study Design:** Prospective single-blind study.

**Setting:** Tertiary medical center.

**Methods:** The enrolled patients were completed for overnight polysomnography (PSG) and comprehensive ophthalmologic evaluation, including laser speckle flowgraphy (LSFG) for microcirculation of optic nerve head (ONH) before and 3 months after OSA surgery. LSFG measurements were summarized as mean blur rate in all areas (MA), in big vessel area (MV) and in tissue area (MT) of ONH.

**Results:** Twenty-nine patients underwent upper airway surgery were included. Three months after surgery, 75.9% (22/29) patients, including 15 of 20 patients with severe OSA and 7 of 9 patients with moderate OSA had improvement in apnea/hypopnea index (AHI). The major parameters of PSG significantly improved. Regarding the LSFG parameters, MA ( $p = 0.023$ ), MV ( $p = 0.033$ ) and MT ( $p = 0.026$ ) significantly increased 3 months after surgery. Moreover, there were significant differences in MA ( $p = 0.035$ ) and MT ( $p = 0.045$ ) in the AHI-improved subgroup after surgery.

**Conclusion:** The ONH microcirculation significantly improved in the AHI-improved patients with OSA 3 months after upper airway surgery. Upper airway surgery may ameliorate the ONH microcirculation in patients with OSA.

**Keywords:** snoring, obstructive sleep apnea syndrome, obstructive sleep apnea surgery, laser speckle flowgraphy, optic nerve head microcirculation

## Introduction

Obstructive sleep apnea/hypopnea syndrome (OSA) is presented by recurrent complete or partial upper airway obstruction during sleep, which often leads to severe hypoxemia and intermittent tissue hypoxia. Intermittent hypoxia can increase sympathetic tone and cause oxidative stress and inflammation. Oxidative stress can induce endothelin-1 and nitric oxide imbalance, and result in vascular dysregulation and endothelial dysfunction.<sup>1-4</sup> Untreated patients with OSA may suffer from cardio- and cerebro-vascular disorders, cognitive dysfunction, motor vehicle accidents and even sudden death.<sup>5-7</sup>

The ocular manifestations, including floppy eyelid syndrome, blepharochalasis, keratoconjunctivitis, non-arteritic anterior ischemic optic neuropathy, papilledema, and normal-tension glaucoma (NTG), had been reported in OSA patients.<sup>8-15</sup> In our previous study, we found that patients with moderate and severe OSA had a higher prevalence of

NTG than in normal subjects and patients with mild OSA.<sup>14</sup> We also found patients with moderate/severe OSA had thinner retinal nerve fiber layer (RNFL) than patients with mild OSA and normal subjects.<sup>16</sup> Repeatedly respiratory disturbances often lead to severe hypoxemia, tissue hypoxia, and reoxygenation, which can induce oxidative stress, free radical formation, and vascular inflammation.<sup>1–4</sup> Chronic vascular inflammation results in endothelial dysfunction and impairment of vascular autoregulation, which can reduce cerebral blood supply and alter blood flow to the ONH, and may further compromise the structure and function of the optic nerve and retina.

Continuous positive airway pressure (CPAP) is the most commonly recommended method for treating OSA. Some patients with OSA who could not tolerate or accept the CPAP treatment will consider other alternatives. Weight loss and lifestyle modifications are highly recommended in all obese or overweight patients. Mandibular advancement devices, positional therapy and hypoglossal nerve stimulation are recent and personalized alternative therapies.<sup>17</sup> Besides, surgery for OSA with a multilevel approach, including oropharyngeal and hypopharyngeal surgical modality, is a substitute for CPAP in clinic practice. The success rate of multilevel upper airway surgery for OSA had improved to 66.4% by meta-analysis.<sup>18,19</sup> Treatment for obstructive respiratory disturbances can alleviate airway obstruction and improve oxygenation during sleep.

The main purpose for treating OSA is not only to improve the polysomnographic parameters and reduce the patients' snoring intensity, but also alleviate the possible adverse consequences of OSA. Hashim et al reported that 5.1% poorly controlled patients with OSA would be diagnosed as NTG after follow up for 3 years. They suggested that severe OSA is an important risk factor for developing glaucoma, and combined OSA and ophthalmic treatment can provide good control of glaucoma.<sup>20</sup> In our previous study, we found that the visual sensitivity, RNFL thickness, and macular layer thickness were significantly increased after CPAP treatment at three months in patients with OSA under good CPAP adherence.<sup>21</sup> In another study, we found that the oxygenation status, visual sensitivity, and macular layer thickness significantly increased 6 months after upper airway surgery in patients with severe OSA.<sup>22</sup> Since OSA treatment improves oxygenation during sleep, we assume that the vascular resistance may decrease and ocular blood flow may ameliorate in treated patients with OSA.

Laser speckle flowgraphy (LSFG) uses the laser speckle phenomenon to noninvasively measure the ocular blood flow. The device is equipped with a diode laser which is applied to the ONH and retina. The light generated in the ONH and retina is scattered to produce speckle patterns on the imaging plane. The moving erythrocytes reflecting the light can blur the speckles. LSFG is a new and innovated measurement of the relative erythrocytes velocity and is expressed in arbitrary units. Besides, LSFG can monitor the changes of blood flow in the same retinal or choroidal vessels and tissue over time. The waveform profiles changing with the heartbeat can be also assessed.<sup>23–26</sup>

In the present study, we use LSFG to assess ONH microcirculation in patients with OSA before and 3 months after upper airway surgery. To our knowledge, this is the first study to evaluate the effect of OSA surgery on ONH microcirculation.

## Patients and Methods

### Study Design

This prospective study was approved by the Institutional Review Board and Ethics Committee of the Chang Gung Memorial Hospital, Taiwan (CGMH IRB: 202201294B0), and followed the tenets of the Declaration of Helsinki. The study hospital, Kaohsiung Chang Gung Memorial Hospital, is a medical center and a tertiary referral hospital with 2600 beds that provide medical care for the population of three million in southern Taiwan. Informed consent was obtained from all participants.

The inclusion criteria for the participants included: age  $\geq 20$  years old, significant symptoms of habitual snoring and/or excessive daytime somnolence, no previous upper airway surgical treatment for sleep-related breathing, failure or refusal of attempts for conservative OSA treatments, such as mandibular advancement devices or CPAP, and body mass index (BMI)  $< 35 \text{ kg/m}^2$ . Participants with the following conditions were excluded: age  $< 20$  or  $> 70$  years old, moderate to severe heart failure (New York Heart Association class III and IV), severe central or peripheral neurological disorders, previous history of upper airway surgical treatment for OSA, currently undergoing conservative OSA treatments, such as

mandibular advancement devices or CPAP,  $\text{BMI} \geq 35 \text{ kg/m}^2$ , contraindications for OSA surgery under general anesthesia, chronic use of sleep pills. Participants who had a history of chronic uveitis, glaucoma, optic neuropathy, and previous ocular trauma or surgeries were also excluded from this study.

Each participant received a detailed interview regarding his/her personal disease(s) and physical examination. All of the participants then underwent a comprehensive full-night polysomnography (PSG) study for the diagnosis of OSA and subsequently referred for a comprehensive ophthalmological examination at the ophthalmologic clinic.

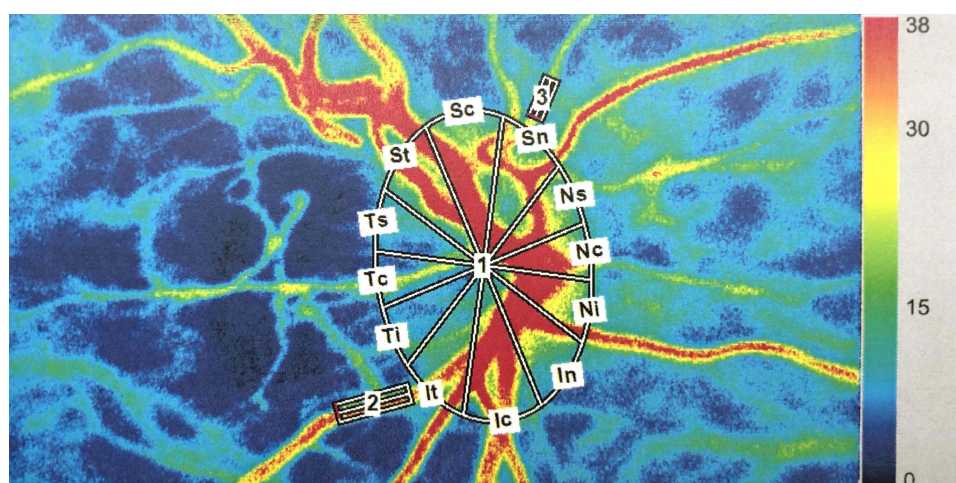
## Sleep Study (Polysomnography, PSG)

The procedure was performed similarly as in our previous studies.<sup>21,22</sup> Obstructive apnea was defined as a cessation of airflow for at least 10 seconds with effort to breathe during apnea. Obstructive hypopnea was defined as an abnormal respiratory event with at least a 30% reduction in thoraco-abdominal movement or airflow when compared to the baseline, lasting at least 10 seconds, and with  $\geq 4\%$  oxygen desaturation. Apnea/hypopnea index (AHI; /hour) was defined as the total number of apneas and hypopneas per hour of electroencephalographic sleep. The severity of OSA is classified according to the AHI during sleep, and OSA is defined as an  $\text{AHI} \geq 5$ . Participants with an AHI between 5 and 15 are classified as mild OSA, an AHI between 15 and 30 is classified as moderate OSA, and an  $\text{AHI} \geq 30$  is classified as severe OSA.<sup>27</sup> All PSGs were scored and read by a board-certified physician who was unaware of the study and blinded to the patients' ophthalmic evaluation results.

## Ophthalmologic Examination

At the time of the ophthalmologic exam, the PSG data was unknown to the participants and the examiner. All participants received ophthalmologic evaluation, including intraocular pressure (IOP) measurement by noncontact tonometry, best-corrected visual acuity, slit-lamp biomicroscopy, fundoscopy, color fundus photography and LSFG measurement.

LSFG exam was performed with the commercially available LSFG-RetFlow (Nidek Co., LTD, Japan). It consists of a fundus camera equipped with an 830-nm diode laser and a fixation target. The devices measure an area of 22 degrees at the retina and a total of 120 frames are recorded for 4 seconds. The built-in analysis software averages all frames and the four-heartbeat data are converted into one-heartbeat data after analysis. A composite color-coded map is generated to show the vascular distribution of the ONH and retina (Figure 1). To evaluate the blood flow at the ONH, we identified the ONH borders for all participants by semi-manually drawing an elliptical region which was compared the color fundus photography (TRC-50EX, TOPCON, Japan). The delineation of the ONH border was performed in all LSFG images by a well-trained operator. Mean blur rate (MBR) is the main parameter of LSFG for the quantification of microcirculation in ONH. It is a quantitative index of blood flow velocity in the target tissue and is used to measure the relative blood flow



**Figure 1** The color-coded composite map of the optic nerve head (ONH). The elliptical region was set semi-manually at the outer edge of the ONH. The colors represent the time averages of MBR over one heartbeat.

in ONH, choroid, and retinal vessels.<sup>23–26</sup> Three MBR parameters were calculated for the ONH microcirculation. MA indicates MBR in all areas, MV indicates MBR in big vessel area, and MT indicates MBR in tissue area of ONH.

The waveform parameters of flow velocity, including blow out time (BOT), blowout score (BOS), acceleration time index (ATI), skew, and fluctuation were also assessed. BOT indicates the time which the wave maintained more than half of the mean of the maximum and minimum MBR during a heartbeat. It means the duration of high-volume blood flow. High BOT indicates well-maintained perfusion during the cardiac cycle. BOS is calculated from the difference of the maximum and the minimum MBR and the average MBR. It means the amount of blood maintaining in the vessels in a heartbeat. A high BOS indicates a high constancy of blood flow during the cardiac cycle. ATI is defined as the ratio of time to reach the peak of MBR and the duration of the heartbeat. ATI is a maximum blood flow index in a heartbeat, which indicates the efficiency of vascular responsiveness. Skew indicates the asymmetric distribution of the MBR waveform. A positive value means a leftward distribution, 0 means a perfectly symmetrical waveform, and a negative value means a rightward distribution. A high skew value indicates arteriosclerosis. Fluctuation describes the dimension of the amplitude of the waveform curve.<sup>24–26</sup>

Systemic evaluation included systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements. The mean arterial pressure (MAP) was calculated as the formula:  $DBP + 1/3 (SBP - DBP)$ , and the ocular perfusion pressure (OPP) was calculated as the formula:  $2/3 MAP - IOP$ .

All patients with OSA received ophthalmologic evaluation before and 3 months after upper airway surgery. The flowchart of the study participant selection process was shown in [Figure 2](#).

## Surgical Procedures

All surgical procedures were performed by the corresponding author (H-C Lin) under general anesthesia. The techniques used were determined at the discretion of the treating sleep surgeon according to the findings on the severity of OSA disease with PSG and the condition of upper airway abnormality with the flexible fibroscopic examination and propofol-induced sleep endoscopy. The surgical techniques are as our previous literature.<sup>28,29</sup>

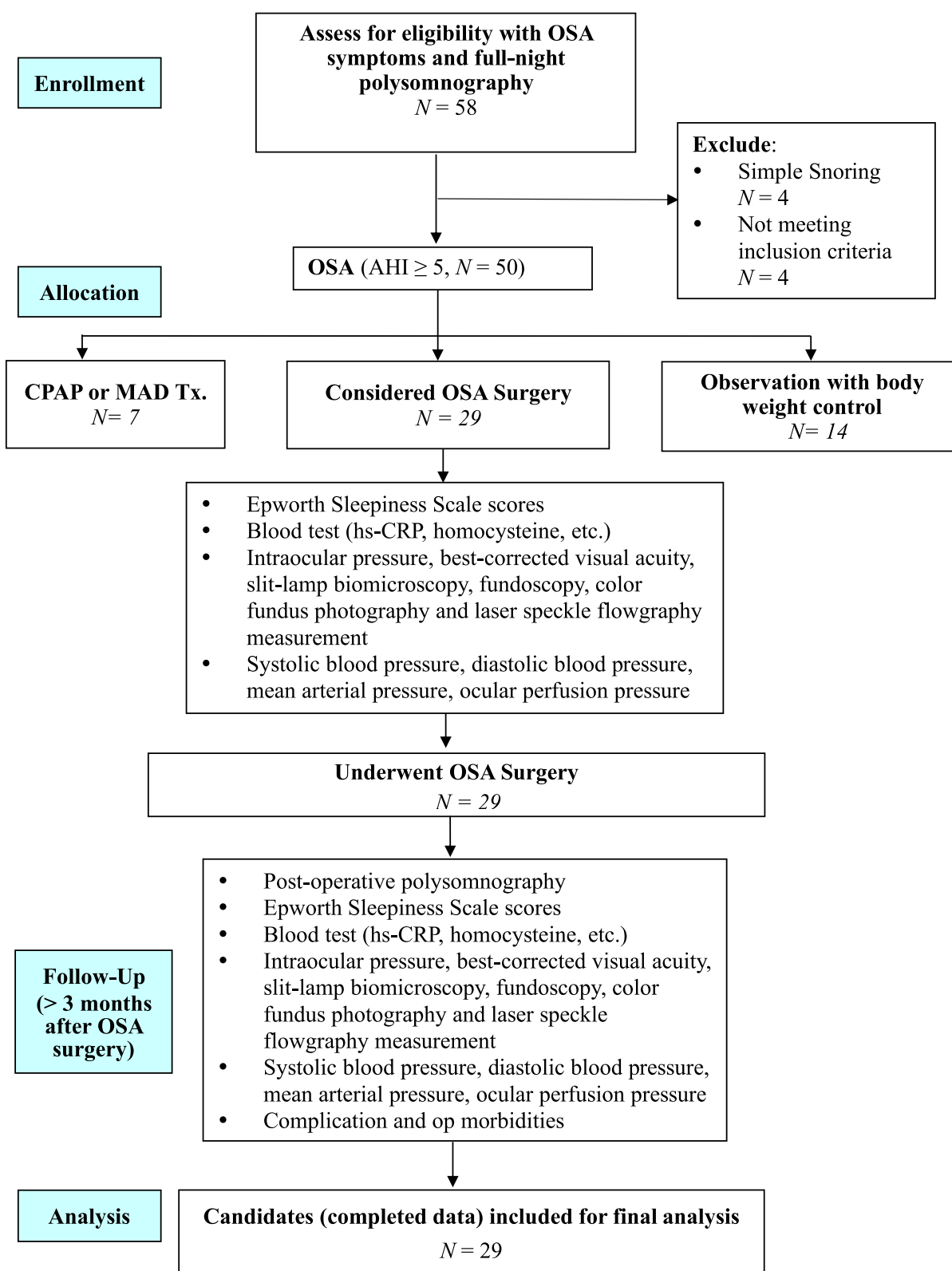
## Statistical Analysis

All analyses were performed using MedCalc<sup>®</sup> Statistical Software version 22.013 (MedCalc Software Ltd, Ostend, Belgium). Continuous data are expressed as mean  $\pm$  standard deviation and categorical variables are expressed as numbers. Continuous data between pretreatment and post-treatment are expressed as mean  $\pm$  standard deviation and compared using paired samples *t*-test. Right eye of each patient was selected for analysis of LSFG parameters. All statistical tests were two-sided. A *p* value  $<0.05$  was considered significant.

## Results

Fifty-eight participants underwent PSG and ophthalmologic examination for this study. Among the participants, 4 were diagnosed as simple snoring with an AHI  $< 5$  and 54 were diagnosed as OSA with an AHI  $\geq 5$ . One OSA patient with glaucoma and 3 with previous refractive surgeries were excluded. Of the 50 OSA patients, 7 received CPAP or mandibular advancement devices treatment and 14 asked to keep observation (8 mild OSA, 5 moderate OSA, and 1 severe OSA) were excluded from this study. A total of 29 OSA patients received upper airway surgery, including 9 patients with moderate OSA and 20 patients with severe OSA. The demographic data are shown in [Table 1](#).

Twenty-two of 29 patients (75.9%), including 7 of 9 patients with moderate OSA and 15 of 20 patients with severe OSA had AHI improvement at 3 months postoperatively. The average AHI improvement was  $19.3 \pm 22.2/\text{hr}$ . ( $p = 0.0002$ ). In comparison of the PSG variables between pretreatment and post-treatment, significant improvements were also noted in Epworth Sleepiness Scale scores, mean saturation of oxygen, lowest saturation of oxygen and desaturation index. Regarding the LSFG parameters, there were significant differences in MA ( $p = 0.023$ ), MV ( $p = 0.033$ ) and MT ( $p = 0.026$ ) between pretreatment and post-treatment, but there were no significant differences in the waveform parameters. We further compared the changes of MA, MV and MT in AHI-improved subgroup (22 patients) and in AHI-non-improved subgroup (7 patients). There were significant differences in MA ( $p = 0.035$ ) and MT ( $p = 0.045$ ) between



**Figure 2** The flowchart of the study participant selection process.



**Table 1** Demographic Data of Patients with Obstructive Sleep Apnea/Hypopnea Syndrome

	OSA (n = 29)
Age (yr.)	36.1 ± 6.8
Sex (M/F)	25/4
Moderate OSA	9
Severe OSA	20
Neck circumference (cm)	38.8 ± 3.1
Smoking	8
Hyperlipidemia	15
DM	0
Hypertension	3
Anti-hypertensives	2 (1 used Valsartan, 1 used Nebivolol)

**Note:** Continuous data were expressed as mean ± standard deviation.

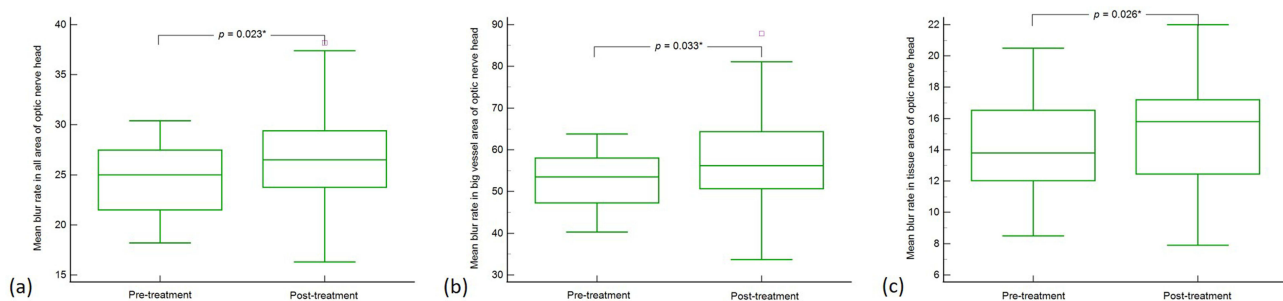
**Abbreviations:** OSA, obstructive sleep apnea/hypopnea syndrome; DM, Diabetes Mellitus.

pretreatment and post-treatment in the AHI-improved subgroup, but there were no significant differences in the AHI-non-improved subgroup. The above data are shown in Figure 3 and Tables 2, 3.

## Discussion

To the best of our knowledge, this is the first study to evaluate the effects of OSA surgery on ONH microcirculation. In this study, we found there were significant improvements of ONH blood flow after upper airway surgery, especially in the AHI-improved subgroup.

Patients with OSA suffer from intermittently complete or partial occlusion of upper airway during sleep. Recurrent sleep apneas cause oxygen desaturation, repeated arousals and episodic nocturnal sympathetic activation, which can increase vascular resistance and decrease blood flow. Besides, hypoxemia and tissue hypoxia can induce formation of oxygen-free radicals at the systemic and tissue levels and result in oxidative stress which induce vascular inflammation and result in endothelial damage and dysfunction.<sup>1-3</sup> Endothelial dysfunction can further impair autoregulation of cerebral and retinal blood flow, increase vascular resistance, and diminish blood flow, which lead to unstable ocular perfusion and compromise the optic nerve and macular function in patients with OSA.<sup>30,31</sup> In our recent study, we found microcirculation of ONH, including MA, MV, MT measurements, were decreased in patients with severe OSA as compared to subjects without OSA and those with mild/moderate OSA. Moreover, decreased blood flow of ONH significantly correlated with OSA severity.<sup>31</sup> Accordingly, treatment of OSA to increase oxygen supply during sleep can reduce oxidative stress, vascular inflammation, endothelial damage, and sympathetic activation, which could be the



**Figure 3** Box plots of MBR parameters for the surgery group. (a) MA, (b) MV, (c) MT. \*Statistically significant.

**Abbreviations:** MBR, mean blur rate; MA, mean blur rate in all areas of optic nerve head; MV, mean blur rate in big vessel area of optic nerve head; MT, mean blur rate in tissue area of optic nerve head.



**Table 2** Comparison of Pre-Treatment and Post-Treatment Polysomnographic Variables, Intraocular Pressure, Blood Pressure, and Laser Speckle Flowgraphy Variables in OSA Patients (n = 29)

	Pre-Treatment	Post-Treatment	P values
ESS	10.4 ± 5.1	8.0 ± 3.4	0.013
AHI (/hr.)	47.3 ± 23.8	28.0 ± 24.0	0.0002*
Longest apnea (sec.)	55.2 ± 23.8	52.9 ± 34.8	0.575
mO <sub>2</sub> (%)	93.7 ± 2.5	94.6 ± 1.3	0.010*
LSaO <sub>2</sub> (%)	77.1 ± 10.7	83.3 ± 7.9	0.0003*
DeS Index (/hr.)	39.8 ± 25.7	22.3 ± 18.0	0.0002*
IOP (mmHg)	15.1 ± 3.2	14.3 ± 3.0	0.082
SBP (mmHg)	131 ± 12	126 ± 11	0.076
DBP (mmHg)	89 ± 12	86 ± 9	0.236
MAP (mmHg)	103 ± 11	99 ± 9	0.144
OPP (mmHg)	53.3 ± 8.0	52.0 ± 6.10	0.359
MA	24.5 ± 3.6	26.8 ± 5.3	0.023*
MV	52.9 ± 6.4	58.0 ± 11.8	0.033*
MT	14.2 ± 3.1	15.1 ± 3.6	0.026*
BOT	55.2 ± 3.3	55.7 ± 4.2	0.550
BOS	81.8 ± 3.8	82.1 ± 3.9	0.704
Skew	10.8 ± 1.8	10.5 ± 2.0	0.397
ATI	29.3 ± 3.8	28.2 ± 5.4	0.172
Fluctuation	10.4 ± 2.4	10.1 ± 2.4	0.480

**Note:** \*Statistically significant by paired samples t-test.

**Abbreviations:** OSA, obstructive sleep apnea/hypopnea syndrome; ESS, Epworth Sleepiness Scale scores; AHI, apnea/hypopnea index; mO<sub>2</sub>, mean saturation of oxygen; LSaO<sub>2</sub>, lowest saturation of oxygen; DeS index, desaturation index; IOP, intraocular pressure; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MAP, Mean arterial pressure; OPP, Ocular perfusion pressure; MA, mean blur rate in all areas of optic nerve; MV, mean blur rate in big vessel area of optic nerve; MT, mean blur rate in tissue area of optic nerve; BOT, blow out time; BOS, blow out score; ATI, Acceleration time index.

**Table 3** Comparison of Pre-Treatment and Post-Treatment Laser Speckle Flowgraphy Variables in the AHI-Improved Group (n = 22) and AHI-Non-Improved Group (n = 7)

	AHI Improved Group (n = 22)			AHI Non-Improved Group (n = 7)		
	Pre-Treatment	Post-Treatment	P values	Pre-Treatment	Post-Treatment	P values
<b>MA</b>	24.2 ± 3.8	26.7 ± 5.2	0.035*	25.2 ± 3.3	27.4 ± 6.4	0.265
<b>MV</b>	52.5 ± 7.0	58.2 ± 12.4	0.066	53.9 ± 5.5	59.3 ± 11.0	0.218
<b>MT</b>	14.0 ± 3.2	14.9 ± 3.2	0.045*	14.4 ± 3.1	15.8 ± 4.9	0.231

**Note:** \*Statistically significant by paired samples t-test.

**Abbreviations:** OSA, obstructive sleep apnea/hypopnea syndrome; MA, mean blur rate in all areas of optic nerve; MV, mean blur rate in big vessel area of optic nerve; MT, mean blur rate in tissue area of optic nerve.

possible mechanism for improving ocular blood flow and avoiding subsequent damage to optic nerve and macular function.

CPAP is the main treatment modality for patients with OSA; however, a certain number of patients with OSA cannot tolerate CPAP. Although other conservative therapies such as mandibular advancement devices, sleep hygiene, and sleep positioning could have benefits for some patients with OSA, there are still many OSA patients with OSA who fail conservative treatments and ask for OSA surgery. Patients with OSA who fail conservative treatments may choose salvage OSA surgery, which creates a non-collapsed airspace, reduce airway resistance, and maintain adequate airflow with normal inspiratory effort during sleep. Most patients with OSA indeed have multilevel disease, and multilevel surgery can effectively relieve the upper airway obstruction.<sup>18,19</sup>

This study was performed at a tertiary medical center, a greater proportion of patients with severe OSA were included than other severities. Most of patients with OSA initially tried CPAP treatment; however, some of them failed to receive CPAP treatment and asked OSA surgery as an alternative. Our results showed that 75.9% patients, including 15 of 20 patients with severe OSA and 7 of 9 patients with moderate OSA who received multilevel surgery had improvement in AHI at 3 months. The average percentage of AHI improvement was 38.2%, and the average improvements of mean saturation of oxygen and lowest saturation of oxygen were  $1.05 \pm 1.98\%$  and  $9.38 \pm 13.7\%$ , respectively. The major PSG data showed significant improvements in oxygenation. In addition, there were significant improvements of ONH blood flow after upper airway surgery, especially in the AHI-improved subgroup. Previous studies also showed that CPAP, oral appliance, or surgery can reduce hypoxia and oxygen desaturation.<sup>32–34</sup> It will be reasonable to presume that the improvement of oxygenation after OSA surgery could reduce oxidative stress and vascular inflammation, resulting in increase of ONH blood flow in the present study.

Previous studies reported that patients with OSA had a high prevalence of glaucoma.<sup>13–15</sup> In our previous study with 247 patients with OSA, we found that the prevalence of NTG in patients with OSA was 5.7%, and the prevalence was even significantly higher in patients with moderate/severe OSA (7.2%).<sup>14</sup> Hashim et al found that 5.1% poorly controlled patients with OSA were diagnosed as NTG after 3 years' follow-up.<sup>20</sup> Furthermore, Lin et al conducted the study using a nationwide, longitudinal population-based dataset in Taiwan to analyze the prevalence and risk of open-angle glaucoma among patients with OSA during a 5-year follow-up period. Their results were that the incidence rate per 1000 person-years was 11.26 (95% confidence interval [CI], 8.61–14.49) and 6.76 (95% CI, 5.80–7.83) for subjects with and without OSA, respectively. After adjusting the possible variables such as diabetes, hypertension, coronary heart disease, and obesity, the hazard ratio for glaucoma within the first 5-year period for subjects with OSA was 1.67 ( $p < 0.001$ ) that of comparison subjects.<sup>35</sup> Repeated hypoxia and hypoxemia in patients with OSA can compromise optic nerve function and increase the risk of glaucoma. Treatment of OSA with CPAP, mandibular advancement devices and multilevel surgery can ameliorate upper airway obstruction and increase oxygenation during sleep. Moreover, ONH microcirculation can also be improved after upper airway surgery. Accordingly, the hypoxia-related abnormalities could be alleviated and the risk of glaucoma can be reduced after OSA treatment.

One of the major limitations of this study is that the sample size was small. Additionally, a greater proportion of patients with severe OSA were included than other severities because the study was performed at a tertiary medical center. Most of the patients with OSA in the surgery group got an improvement in AHI and PSG variables. Besides, male gender predominated in our study due to males are more common than females for OSA occurrence. Further studies for age-matched and gender-matched subgroups with different severities of OSA are needed. Moreover, personal history of systemic hypertension or antihypertensive medication use might have some effects on blood flow measurements. However, all the surgery patients did not change their medication after OSA surgery. There may be little effect before and after treatment. Furthermore, we evaluated the LSFG variables only 3 months after multilevel upper airway surgery, further long-term evaluation of these parameters are required to determine the treatment effect on ONH microcirculation. In addition, it would be an interesting future direction to try and tease out the pathophysiology further to determine which aspect of OSA is driving these results to a non-Taiwanese population of patients with OSA.

In conclusion, the ONH microcirculation significantly improved in the AHI-improved patients with OSA 3 months after upper airway surgery in our preliminary study. Upper airway surgery may ameliorate the ONH microcirculation in patients with OSA.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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