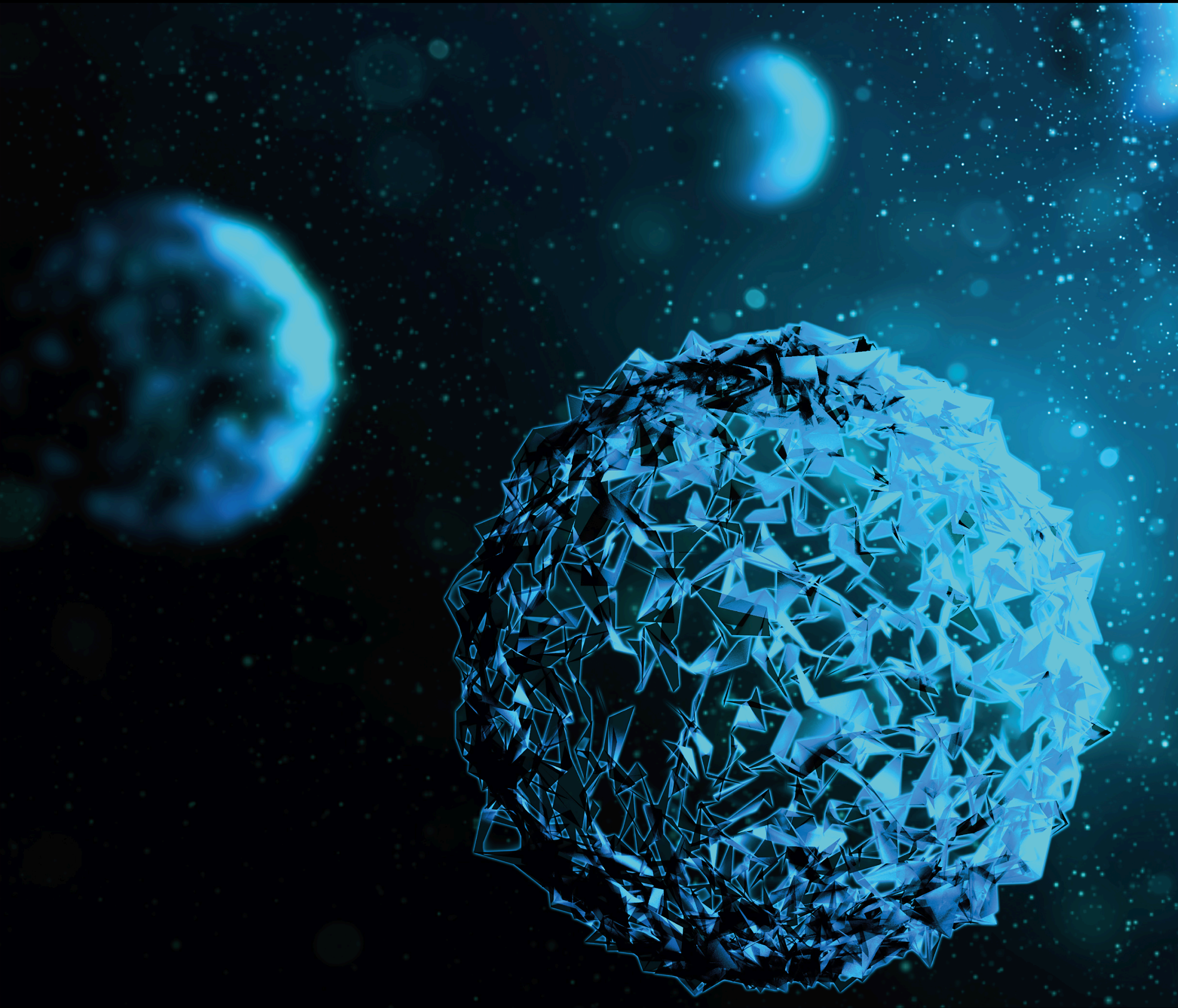
BioMed Research International

Management of Thyroid Eye Disease

Lead Guest Editor: Chieh-Chih Tsai
Guest Editors: Shi-Bei Wu, Hui-Chuan Kau, and Yoon Duck Kim



Management of Thyroid Eye Disease

BioMed Research International

Management of Thyroid Eye Disease

Lead Guest Editor: Chieh-Chih Tsai
Guest Editors: Shi-Bei Wu, Hui-Chuan Kau, and
Yoon Duck Kim

Copyright © 2022 Hindawi Limited. All rights reserved.

This is a special issue published in "BioMed Research International." All articles are open access articles distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Section Editors

Penny A. Asbell, USA
David Bernardo, Spain
Gerald Brandacher, USA
Kim Bridle, Australia
Laura Chronopoulou, Italy
Gerald A. Colvin, USA
Aaron S. Dumont, USA
Pierfrancesco Franco, Italy
Raj P. Kandpal, USA
Fabrizio Montecucco, Italy
Mangesh S. Pednekar, India
Letterio S. Politi, USA
Jinsong Ren, China
William B. Rodgers, USA
Harry W. Schroeder, USA
Andrea Scribante, Italy
Germán Vicente-Rodriguez, Spain
Momiao Xiong, USA
Hui Zhang, China

Academic Editors

Ophthalmology

Susmito Biswas, United Kingdom
Enrico Borrelli, Italy
Juan M. Bueno, Spain
Maddalena De Bernardo, Italy
Anto De Pol, Italy
Luca Di Antonio, Italy
Paolo Fogagnolo, Italy
Ilias Georgalas, Greece
Jose M. González-Meijome, Portugal
Tomoya Handa, Japan
David R. Hinton, USA
Chieko Koike, China
Eri Kubo, Japan
Toshiaki Kubota, Japan
Toshihide Kurihara, Japan
Timothy Y. Lai, Hong Kong
João P. Marques, Portugal
Gen Miura, Japan
Atsushi Mizota, Japan
Rasim Mogulkoc, Turkey
Toshiyuki Oshitari, Japan
Maurizio Battaglia Parodi, Italy
Luisa Pierro, Italy
Barbara K. Pierscionek, United Kingdom
Mohsen Pourazizi, Iran
Gaurav Prakash, USA
Lisa Toto, Italy
Haiwei Xu, China
Alvin L. Young, Hong Kong

Contents

Evaluation of Microcirculation in Optic Nerve Head Using Laser Speckle Flowgraphy in Active Thyroid Eye Disease
Margaret Ming-Chih Ho, Yueh-Ju Tsai, Yen-Chang Chu, and Yi-Lin Liao
Research Article (7 pages), Article ID 9115270, Volume 2022 (2022)

The Changes in Optic Nerve after Orbital Decompression Surgery for Thyroid Eye Disease and Case Reports of Ischemic Optic Neuropathy
Yun Hsia, Chia-Chieh Hsiao, Yi-Hsuan Wei, I-Wen Lai, Chao-Wen Lin, and Shu-Lang Liao
Research Article (10 pages), Article ID 4808194, Volume 2022 (2022)

Hindawi
BioMed Research International
Volume 2022, Article ID 9115270, 7 pages
https://doi.org/10.1155/2022/9115270

Research Article

Evaluation of Microcirculation in Optic Nerve Head Using Laser Speckle Flowgraphy in Active Thyroid Eye Disease

Margaret Ming-Chih Ho,[1] **Yueh-Ju Tsai**,[1,2] **Yen-Chang Chu**,[1,2] **and Yi-Lin Liao**[1,2]

[1]*Department of Ophthalmology, Chang Gung Memorial Hospital, Linkou, Taiwan*
[2]*College of Medicine, Chang Gung University, Taoyuan, Taiwan*

Correspondence should be addressed to Yi-Lin Liao; yilinliao@gmail.com

Received 7 November 2021; Revised 17 January 2022; Accepted 5 February 2022; Published 16 March 2022

Academic Editor: Chieh-Chih Tsai

Copyright © 2022 Margaret Ming-Chih Ho et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Laser speckle flowgraphy (LSFG) can be used to estimate optic nerve blood flow. This study used LSFG to evaluate optic nerve microcirculation in patients with thyroid eye disease (TED). *Methods*. This was a retrospective review of patients with active TED who underwent LSFG between October 2020 and June 2021. The mean blur rate (MBR) for different severities of active TED was analyzed by one-way analysis of variance (ANOVA). *Results*. A total of 30 patients (60 eyes) with a diagnosis of active TED who underwent LSFG were included. The mean age was 49 (range, 33–74) years. Mean best-corrected visual acuity was the worst in the group with sight-threatening active TED (0.29 ± 0.33 logarithm of the minimum angle of resolution, $p = 0.01$). The MBR-overall was the highest in the group with mild active TED (28.5 ± 2.7), followed by that in the moderate to severe (23.6 ± 3.2), and in the sight-threatening (20.2 ± 4.3) active TED groups ($p < 0.001$). The MBR-vessel was 57.1, 47.0, and 39.3 in the mild, moderate to severe, and sight-threatening active TED groups, respectively ($p < 0.001$). The MBR-tissue was 16.9, 14.4, and 12.0 in the mild, moderate to severe, and sight-threatening active TED groups, respectively ($p < 0.001$). *Conclusions*. This study demonstrates that optic nerve blood flow is lower with more severe active TED. In addition, LSFG is an effective, objective, and noninvasive method for evaluating the severity of TED.

1. Introduction

Thyroid eye disease (TED) is an autoimmune inflammatory disease characterized by proptosis, lid retraction, and diplopia (1). TED occurs in 35% (2) of patients with Graves' disease and may affect the patient's appearance, causing ocular discomfort and leading to dysthyroid optic neuropathy (DON). DON, a severe complication of TED, has been demonstrated to occur in 4–8% (3–5) of the population with TED and may lead to a decrease in color vision, visual field defect, and even visual loss without early and prompt management (5, 6).

Currently, the diagnosis of TED is generally based on clinical presentation. The European Group on Graves' Orbitopathy (EUGOGO) classified TED into mild, moderate to severe, and sight-threatening according to the degree of lid retraction, soft tissue involvement, proptosis, and diplopia (7). Visual field changes, relative afferent pupillary defects, diminished color vision, and radiological hypertrophy of the extraocular muscle might also indicate progression of the disease (6, 8). However, as far as we are aware of, none of the aforementioned parameters can be used to objectively quantify the severity of the disease individually. Color Doppler ultrasound has been used to measure orbital blood flow changes in patients with TED, but the relationship between orbital blood flow and the severity of TED remains unclear (9–11).

Laser speckle flowgraphy (LSFG) is based on the laser speckle phenomenon and is a noninvasive instrument that can measure two-dimensional relative blood flow velocity of the ocular microcirculation in real time (12, 13). The mean blur rate (MBR), which represents the velocity of optic nerve blood flow, has been previously applied to monitor the severity of glaucoma (14, 15), evaluate ischemic optic neuropathy (16, 17), and detect retinal diseases (18). Although LSFG can be used to estimate optic nerve blood flow, to the best of our knowledge, it has never been used to monitor blood flow changes in patients with TED or to evaluate the severity of TED.

The aim of this study was to evaluate optic nerve microcirculation through LSFG in patients with active TED of differing degrees of severity. We hypothesized that patients with more severe active TED would have lower MBR, which could be determined using LSFG.

2. Materials and Methods

2.1. Characteristics of Study Patients. This was a retrospective study of patients with active TED who underwent LSFG. Electronic medical charts for patients between October 2020 and June 2021 at Linkou Chang Gung Memorial Hospital, the largest tertiary referral hospital in Taiwan, were reviewed. The study design conformed to the principles of the Declaration of Helsinki and was approved by the Chang Gung Medical Foundation's Hospital Ethics Committee on Human Research (IRB number: 202101159B0).

We recruited patients with active TED. Active TED was defined as an inflammatory score ≥ 4 on the VISA grading system (19). The VISA inflammatory score organizes the clinical features of TED into 4 discrete groupings: V (vision, dysthyroid optic neuropathy), I (inflammation, congestion), S (strabismus, motility restriction), and A (appearance, exposure). Patients with a history of glaucoma, ocular hypertension, ocular surface disease, or optic nerve diseases other than DON were excluded. Patients who could not undergo LSFG were also excluded.

Demographic data and information on previous systemic and ocular diseases, steroid use, surgical treatment for Graves ophthalmopathy, clinical presentations, and comprehensive ocular examination results comprising best-corrected visual acuity (BCVA), intraocular pressure, Hertel exophthalmometry, the Ishihara color test, and the diplopia test were obtained from participants' medical records. BCVA was measured using the Snellen chart. Mean arterial pressure (MAP) was calculated as $\mathrm{DBP} + 1/3(\mathrm{SBP} - \mathrm{DBP})$, and mean ocular perfusion pressure (MOPP) was calculated as $2/3[\mathrm{DBP} + 1/3\ (\mathrm{SBP} - \mathrm{DBP}) - \mathrm{IOP}]$ (20, 21).

2.2. EUGOGO Classification. Patients with active TED were divided into groups by EUGOGO classification (7). The EUGOGO classifies TED severity as follows:

(1) TED is considered mild if the patient has one or more of the following

(i) Minor lid retraction (<2 mm)
(ii) Mild soft-tissue involvement
(iii) Exophthalmos <3 mm above normal for race and gender
(iv) No or intermittent diplopia with corneal exposure responsive to lubricants

(2) TED is considered moderate to severe if the patient has two or more of the following

(i) Lid retraction of ≥2 mm
(ii) Moderate or severe soft-tissue involvement
(iii) Exophthalmos ≥3 mm above normal for race and gender
(iv) Intermittent or constant diplopia

(3) TED is considered sight-threatening if the patient has previously experienced DON and/or corneal breakdown

2.3. LSFG and Clinical Settings. All the patients in our study underwent LSFG. The instrument was equipped with a fundus camera with a diode laser (wavelength, 830 μm) as the light source and a charge-coupled sensor (750 pixels wide × 360 pixels high) as the detector. A speckle pattern is produced by the laser, whose interference is scattered by the movements of erythrocytes; the interference pattern can be detected by the detector. MBR, acquired at 30 frames/second over a 4 second period, represents the velocity of optic nerve head (ONH) blood flow (Figure 1). MBR can be expressed as overall MBR (MBR-overall) or divided into that of the vessel areas (MBR-vessel) or tissue areas (MBR-tissue).

In our study, the patients' heart rate, systolic blood pressure, and diastolic blood pressure were measured after the patients had rested in a quiet room for 10 minutes before LSFG. MBR values were measured with the LSFG RetFlow (NIDEK Co., Ltd. Gamagori, Aichi, Japan). Both eyes of the patients were measured. An average of three successive measurements in each eye was required to determine MBR values.

2.4. Statistical Analyses. Descriptive statistics were used to evaluate patient demographics and baseline clinical examination results at the time of presentation. The intraocular pressure in upward gaze, MBR-overall, MBR-vessel, and MBR-tissue following normal distributions was analyzed through one-way analysis of variance (ANOVA). Because the patients' BCVA, age, and intraocular pressure in primary gaze did not follow a normal distribution, the Kruskal–Wallis test was used to evaluate differences among the active TED severity groups. Independent t tests or Mann–Whitney U tests were used to evaluate the differences between any two active TED severity groups. A chi-squared test was used to evaluate sex differences among TED severity groups. The significance level was set at $p = 0.05$. Statistical analyses were

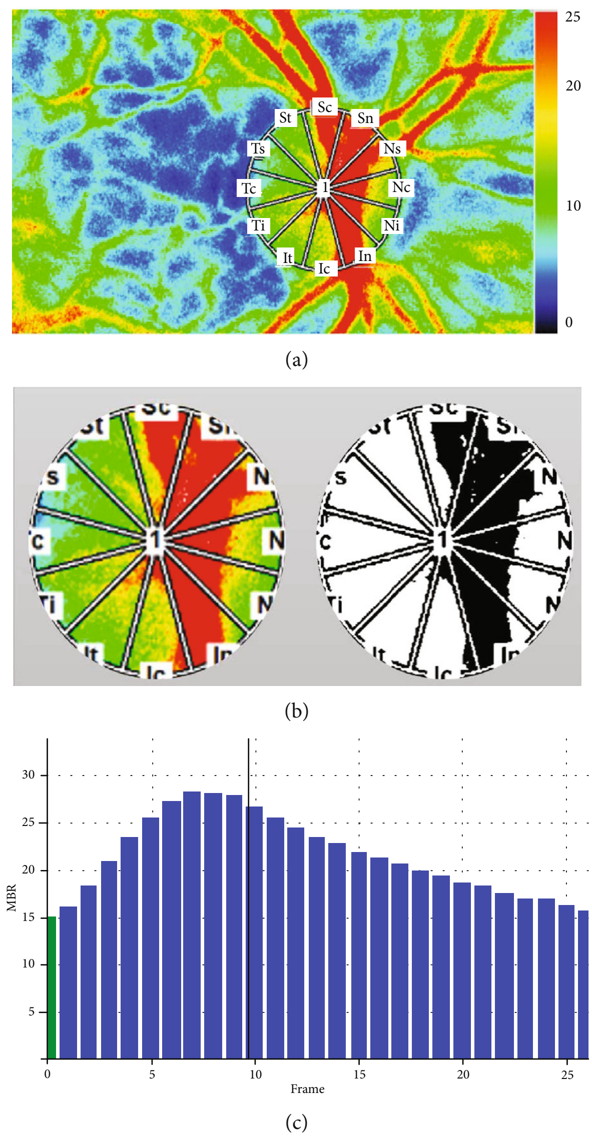


Figure 1: Analysis of pulse waveforms for the optic nerve head (ONH) using laser speckle flowgraphy (LSFG). (a) A representative color-coded composite map was used to record the mean blur rate (MBR). Red represents high MBR, and blue represents low MBR. (b) MBR was calculated by placing a rubber band around the ONH. The segmentation of the vessel area (black area) and tissue area (white area) of the ONH is shown in binary format. (c) A pulse waveform of MBR for one cardiac cycle.

performed using MedCalc Statistical Software version 20.009 (MedCalc Software Ltd., Ostend, 2021).

3. Results

A total of 54 patients with a diagnosis of TED who underwent LSFG were included. However, 19 were excluded because of inactive TED (VISA inflammatory score < 4), and five were excluded because of incomplete medical records. Therefore, 30 patients (60 eyes: 11 male and 19 female) were included. The mean age was 49 years (range, 33–74 years).

3.1. Clinical Characteristics in Different TED Severity Groups. The clinical characteristics and MBRs of the different TED severity groups are listed in Table 1. Mild, moderate to severe, and sight-threatening TED accounted for 12 (20%), 31 (52%), and 17 (28%) eyes, respectively. The mean age of the sight-threatening TED group was 57.3 years, higher than both the moderate to severe (46.8 years) and the mild (42.6 years) TED groups ($p = 0.003$). Differences in the prevalence of smoking among the different groups were not observed ($p > 0.999$). Of the patients who received high-dose intravenous steroid treatment, 12 (70.6%) were in the sight-threatening TED group, 15 (48.4%) in the moderate to severe TED group, and 3 (25%) were in the mild TED group. Five patients (29.4%) in the sight-threatening group had a history of orbital decompression, whereas one patient (3.2%) in the moderate to severe group had such a history.

Mean systolic blood pressure in the three groups was 98.5 ± 34.6, 140.4 ± 24.4, and 122.3 ± 22.8 mmHg in the mild, moderate to severe, and sight-threatening groups,

Table 1: Clinical characteristics and MBR in active thyroid eye disease group.

	Mild		Moderate to severe		Sight-threatening		p value
No. of eyes, n (%)	12		31		17		
Age, mean (SD)	42.6	(10.0)	46.8	(12.7)	57.3	(11.2)	0.003∗
Gender, male (%)	2	(16.7)	15	(48.4)	4	(23.5)	0.074
Smoking, n (%)	1	(0.1)	3	(0.1)	1	(0.1)	>0.999
History of high-dose intravenous steroid treatment, n (%)	3	(25.0)	15	(48.4)	12	(70.6)	0.052
History of orbital decompression, eyes (%)	0	(0)	1	(3.2)	5	(29.4)	0.014∗
Systemic findings							
SBP, mmHg, mean (SD)	98.5	(34.6)	140.4	(24.4)	122.3	(22.8)	0.002∗
DBP, mmHg, mean (SD)	86.2	(20.9)	82.3	(15.1)	74.0	(10.5)	0.503
MAP, mmHg, mean (SD)	85.5	(10.3)	100.7	(15.3)	90.1	(12.3)	0.119
MOPP, mmHg, mean (SD)	59.8	(34.2)	49.9	(10.5)	40.4	(8.7)	0.364
HR, bpm, mean (SD)	68.8	(14.6)	69.8	(9.2)	62.5	(11.6)	0.890
Ocular findings							
BCVA (logMAR), mean (SD)	0.08	(0.1)	0.08	(0.2)	0.29	(0.3)	0.005∗
IOP (primary gaze), mean (SD), mmHg	15.3	(3.8)	18.8	(4.9)	19.5	(3.4)	0.031∗
IOP (upward gaze), mean (SD), mmHg	19.4	(4.0)	22.7	(5.2)	25.7	(4.9)	0.033∗
MBR, mean (SD)							
MBR-overall	28.5	(2.7)	23.6	(3.2)	20.2	(4.3)	<0.001†
MBR-vessel	57.1	(8.0)	47.0	(6.9)	39.3	(6.9)	<0.001†
MBR-tissue	16.9	(3.1)	14.4	(2.9)	12.0	(2.7)	<0.001†

∗$p < 0.05$, †$p < 0.001$. BCVA: best-corrected visual acuity; bpm: beats per minutes; DBP: diastolic blood pressure; HR: heart rate; logMAR: logarithm of the minimum angle of resolution; IOP: intraocular pressure; MAP: mean arterial pressure; MBR: mean blur rate; mmHg: millimeter of mercury; MOPP: mean ocular perfusion pressure: SBP: systolic blood pressure; SD: standard deviation.

respectively ($p = 0.002$); mean diastolic blood pressure was 86.2 ± 20.9, 82.3 ± 15.1, and 74.0 ± 10.5 mmHg in the mild, moderate to severe, and sight-threatening groups, respectively ($p = 0.503$). MAP was 85.5 ± 10.3, 100.7 ± 15.3, and 90.1 ± 12.3 mmHg in the mild, moderate to severe, and sight-threatening groups, respectively ($p = 0.119$). MOPP was 59.8 ± 34.2, 49.9 ± 10.5, and 40.4 ± 8.7 mmHg the in mild, moderate to severe, and sight-threatening groups, respectively ($p = 0.364$). The mean heart rate was 68.8 ± 14.6, 69.8 ± 9.2, and 62.5 ± 11.6 beats per minute in the mild, moderate to severe, and sight-threatening groups, respectively ($p = 0.890$). The correlation coefficients between clinical characteristics and MBRs are listed in Supplemental Table 1.

3.2. BCVA, Intraocular Pressure, and MBR in the TED Severity Groups. The mean BCVA was the lowest in the sight-threatening group (logMAR 0.29 ± 0.33, $p = 0.01$). The sight-threatening group had the highest mean intraocular pressure in both primary (19.5 ± 3.4 mmHg, $p = 0.03$) and upward gaze (25.7 ± 4.9 mmHg, $p = 0.03$). The MBR-overall was the highest in the mild TED group (28.5 ± 2.7), followed by the moderate to severe (23.6 ± 3.2) and sight-threatening (20.2 ± 4.3) groups ($p < 0.001$; Figure 2(a)). The MBR-vessel was 57.1, 47.0, and 39.3 in the mild, moderate to severe, and sight-threatening groups, respectively ($p < 0.001$; Figure 2(b)), and the MBR-tissue was 16.9, 14.4, and 12.0 in the mild, moderate to severe, and sight-threatening groups, respectively ($p < 0.001$; Figure 2(c)). The statistical difference between each two groups is listed in Supplemental Figure S1. BCVA, intraocular pressure, and MBR values in the three active TED groups are listed in Table 1. The correlation coefficients between the ocular findings and the MBRs are listed in Supplemental Table 1.

4. Discussion

This study reviewed the ONH blood flow in patients with active TED who underwent LSFG measurements. To the best of our knowledge, this is the first study to objectively quantify ONH blood flow using LSFG in TED and statistically identify ocular blood flow changes in different severities of active TED. Using ANOVA, we found that MBR-overall, MBR-vessel, and MBR-tissue were lower in eyes with more severe active TED. The MBR can quantitatively measure blood flow velocity of the ONH in LSFG examinations (14, 15). Lower MBRs may indicate slower ONH blood flow velocities in patients with more severe active TED. Our results support that patient with more severe TED suffered from more ischemic status of optic nerve microcirculation.

Changes in orbital blood flow in patients with TED have been reported in previous studies (9–11, 22–24). Using color Doppler sonography, Somer et al. (23) reported lower mean superior ophthalmic vein blood flow velocity in patients with TED compared with those without TED. Konuk et al. (9) observed a significantly lower superior ophthalmic vein

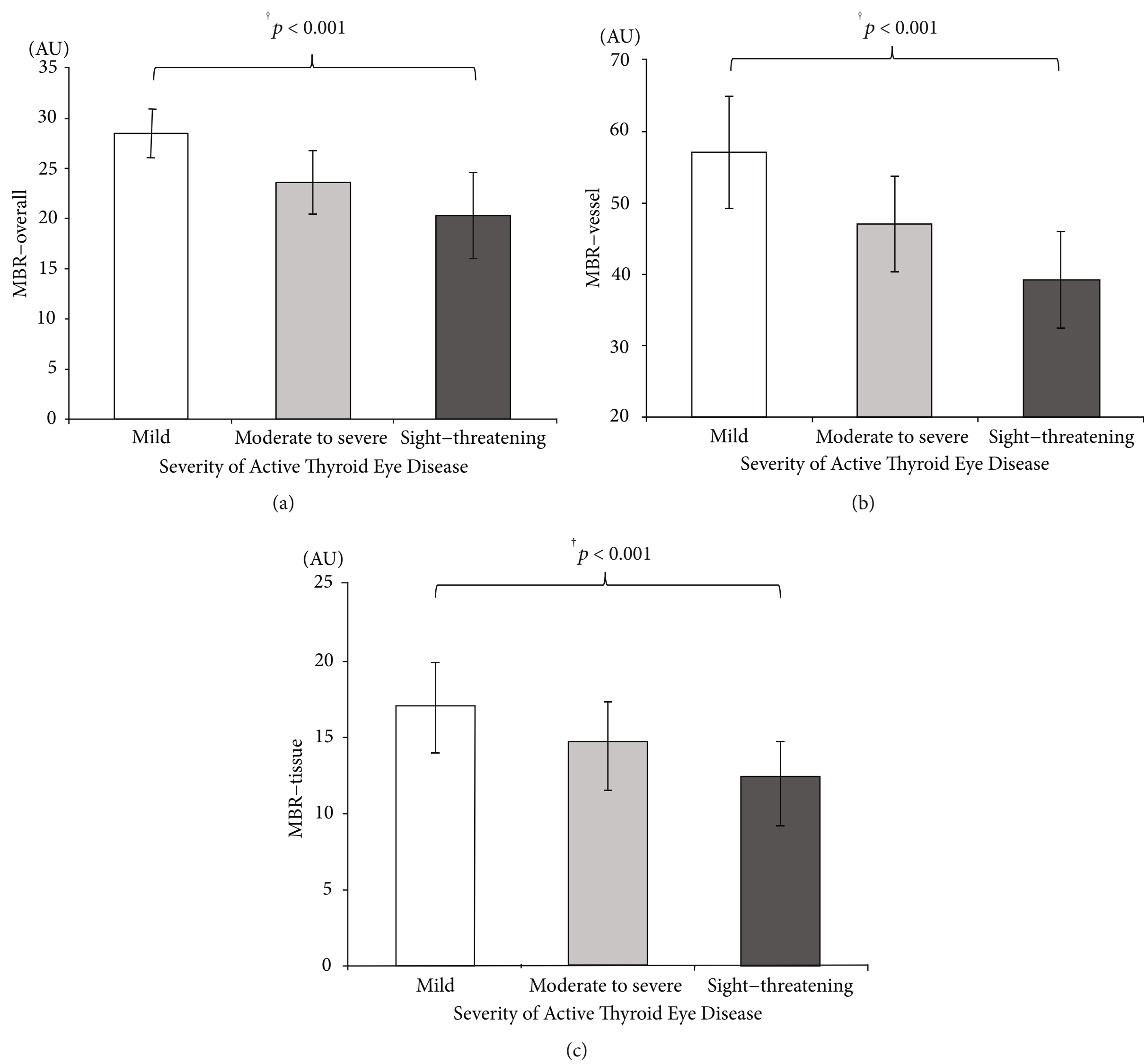


Figure 2: Mean blur rate (MBR) and different severities of active thyroid eye disease (TED). MBR-overall (a), MBR-vessel (b), and MBR-tissue (c) were significantly lower with more severe active TED.

blood flow velocity in patients with sight-threatening TED than in those without sight-threatening TED. Lešin et al. (10) reported a decrease in the flow velocity of the ophthalmic artery and central retinal artery in patients with early sight-threatening TED, which suggested that changes in the orbital vasculature might be the first sign of sight-threatening TED. The decrease in MOPP resulted from a combination of one or more contributing factors, including the inflammatory process, passive compression by enlargement of the extraocular muscles, and increased orbital pressure (25). Using LSFG, we found a prominent trend of lower ocular blood flow velocity at more severity levels of active TED, supporting the theory of vascular insufficiency during the progression of active TED.

MAP is defined as the average arterial pressure throughout one cardiac cycle and can be affected by cardiac output and systemic vascular resistance (20). MOPP is a calculated value that is affected by MAP and IOP. A decrease in MOPP was indicated as a risk factor for the prevalence and progression of glaucoma because such a change may indicate ONH blood flow dysregulation in glaucoma patients (26). However, in patients with active TED, MOPP may be affected by multiple factors, including orbital inflammation, passive compression by enlargement of the extraocular muscles, and increased orbital pressure. MOPP is not an accurate indicator of ocular microcirculation because it is determined solely on the basis of blood pressure and intraocular pressure readings. Nevertheless, using the LSFG examination, we were able to measure the ocular microcirculation quantitatively and objectively, and this may help evaluate patients with active TED.

In comparison with color Doppler imaging (9, 10, 23), the advantages of LSFG are the high reproducibility and objectivity of measurements (27, 28). Furthermore, the penetrating long-wavelength laser used in LSFG may accurately examine the ONH without effects caused by the configuration of the disc. Moreover, LSFG may permit the evaluation of the overall ONH microcirculation rather than that of a single artery or vein, which may help reduce measurement error. A previous study used optical coherence tomography angiography to evaluate choroidal thickness, which can reflect choroidal vasculature changes in active TED (29). However, adequate visualization of the entire choroid is necessary for accurate measurements (30). Because LSFG measures perfusion of only the ONH, the visualization of the choroid is not needed.

In previous studies, age and sex have been considered as factors affecting LSFG results (31, 32). Iwase et al. (32) reported that women had a higher MBR-overall than men. Aizawa et al. (31) found that age was correlated with MBR-vessel and that sex was correlated with both MBR-overall and MBR-vessel. They also discovered that MBR-tissue was independent of both age and sex. In our study, age and TED severity were significantly correlated because of the clinical nature of TED (33). The age differences among groups might partially affect their MBR-overall and MBR-vessel results. However, the MBR-tissue, which is statistically independent of age, was also significantly lower for more severe TED. To further reduce the effects of age variability on our study, we conducted a small subanalysis by matching patients by age, with the difference in matched ages in the subanalysis group being not more or less than 2 years (Supplemental Table 2). In this small subanalysis, the MBR-overall, MBR-vessel, and MBR-tissue were all significantly lower in the severe active TED group. This result demonstrates that the decreases in MBR observed in our study were mainly the result of the severity of the disease rather than the effect of the ages of the patients in each group. Our study did not find a significant correlation between sex and TED severity.

The limitation of this study includes its retrospective nature. Moreover, because this study was conducted at a referral hospital, patients with mild active TED tended to be followed up at local hospitals, which limited the number of cases in the mild TED group. Besides, axial length was not controlled because this was a retrospective study; axial length is not a routine examination for patients with active TED. This may lead to bias due to the potential effect of axial length on MBR. Nevertheless, to the best of our knowledge, this study was the first to demonstrate the relationship between ONH blood flow and the severity of active TED and to use LSFG to evaluate patients with TED. Further longitudinal studies are required to evaluate ONH blood flow changes during TED progression.

5. Conclusions

Active TED has variable clinical manifestations. Our study demonstrates that a decrease in ONH perfusion is correlated with more severe TED. Moreover, LSFG is an effective, objective, and noninvasive method for evaluating patients with TED. We believe that our results may help clinicians to evaluate the severity of active TED more easily and accurately.

Data Availability

The data analyzed during this study are available on request from the corresponding author, Yi-Lin, Liao. The data are not publicly available due to it containing information that could compromise the privacy of research participants.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

All authors have participated directly in planning and execution of the work. MMH did the acquisition and analysis of data, drafting, and writing of the article; YJT and YCC did the acquisition and analysis of data; YLL did the design of the study, acquisition of data, and final approval. All authors read and approved the final manuscript.

Supplementary Materials

Supplementary 1. Supplemental Figure 1: mean blur rate (MBR) and different severities of active thyroid eye disease (TED). MBR-overall (a), MBR-vessel (b), and MBR-tissue (c) were significantly lower with more severe active TED. $^{\dagger}p < 0.001$, $*p < 0.05$, $**p = 0.058$.

Supplementary 2. Supplemental Table 1: Spearman's rank correlation coefficient between clinical parameters and MBR.

Supplementary 3. Supplemental Table 2: Clinical characteristics and MBR in age-matched active thyroid eye disease group.

References

[1] Y. H. Chin, C. H. Ng, M. H. Lee et al., "Prevalence of thyroid eye disease in Graves' disease: a meta-analysis and systematic review," *Clinical Endocrinology*, vol. 93, no. 4, pp. 363–374, 2020.

[2] S. L. Lim, A. K. E. Lim, M. Mumtaz, E. Hussein, W. M. W. Bebakar, and A. S. Khir, "Prevalence, risk factors, and clinical features of thyroid-associated ophthalmopathy in multiethnic Malaysian patients with Graves' disease," *Thyroid*, vol. 18, no. 12, pp. 1297–1301, 2008.

[3] G. B. Bartley, "The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmsted County, Minnesota," *Transactions of the American Ophthalmological Society*, vol. 92, pp. 477–588, 1994.

[4] C. M. Dayan and M. R. Dayan, "Dysthyroid optic neuropathy: a clinical diagnosis or a definable entity?," *British Journal of Ophthalmology*, vol. 91, no. 4, pp. 409-410, 2007.

[5] R. Gupta, R. Thomas, F. Almukhtar, and A. Kiran, "Visual morbidity in thyroid eye disease in Asian Indian patients," *Indian Journal of Ophthalmology*, vol. 68, no. 8, pp. 1622–1627, 2020.

[6] B. Tramunt, P. Imbert, S. Grunenwald, F. Boutault, and P. Caron, "Sight-threatening Graves' orbitopathy: twenty years' experience of a multidisciplinary thyroid-eye outpatient

clinic," *Clinical Endocrinology*, vol. 90, no. 1, pp. 208–213, 2019.

[7] L. Bartalena, G. J. Kahaly, L. Baldeschi et al., "The 2021 European Group on Graves' Orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy," *European Journal of Endocrinology*, vol. 185, no. 4, pp. G43–G67, 2021.

[8] W. M. Wiersinga, P. Perros, G. J. Kahaly et al., "Clinical assessment of patients with Graves' orbitopathy: the European Group on Graves' Orbitopathy recommendations to generalists, specialists and clinical researchers," *European Journal of Endocrinology*, vol. 155, no. 3, pp. 387–389, 2006.

[9] O. Konuk, Z. Onaran, S. Ozhan Oktar, C. Yucel, and M. Unal, "Intraocular pressure and superior ophthalmic vein blood flow velocity in Graves' orbitopathy: relation with the clinical features," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 247, no. 11, pp. 1555–1559, 2009.

[10] M. Lešin, V. Rogošić, L. Vanjaka Rogošić, I. Barišić, and G. Pelčić, "Flow changes in orbital vessels detected with color Doppler ultrasound in patients with early dysthyroid optic neuropathy," *Acta Clinica Croatica*, vol. 57, no. 2, pp. 301–306, 2018.

[11] Y. Nakase, T. Osanai, K. Yoshikawa, and Y. Inoue, "Color Doppler imaging of orbital venous flow in dysthyroid optic neuropathy," *Japanese Journal of Ophthalmology*, vol. 38, no. 1, pp. 80–86, 1994.

[12] K. Yaoeda, M. Shirakashi, S. Funaki, H. Funaki, T. Nakatsue, and H. Abe, "Measurement of microcirculation in the optic nerve head by laser speckle flowgraphy and scanning laser Doppler flowmetry," *American Journal of Ophthalmology*, vol. 129, no. 6, pp. 734–739, 2000.

[13] K. Yaoeda, M. Shirakashi, S. Funaki et al., "Measurement of microcirculation in optic nerve head by laser speckle flowgraphy in normal volunteers," *American Journal of Ophthalmology*, vol. 130, no. 5, pp. 606–610, 2000.

[14] N. Kiyota, H. Kunikata, Y. Shiga, K. Omodaka, and T. Nakazawa, "Ocular microcirculation measurement with laser speckle flowgraphy and optical coherence tomography angiography in glaucoma," *Acta Ophthalmologica*, vol. 96, no. 4, pp. e485–e492, 2018.

[15] G. Calzetti, A. S. Mursch-Edlmayr, A. M. Bata et al., "Measuring optic nerve head perfusion to monitor glaucoma: a study on structure–function relationships using laser speckle flowgraphy," *Acta Ophthalmologica*, vol. 100, no. 1, 2022.

[16] T. Maekubo, H. Chuman, and N. Nao-i, "Laser speckle flowgraphy for differentiating between nonarteritic ischemic optic neuropathy and anterior optic neuritis," *Japanese Journal of Ophthalmology*, vol. 57, no. 4, pp. 385–390, 2013.

[17] H. Takako, C. Hideki, and N.-i. Nobuhisa, "Evaluation of optic nerve head blood flow in normal rats and a rodent model of non-arteritic ischemic optic neuropathy using laser speckle flowgraphy," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 255, no. 10, pp. 1973–1980, 2017.

[18] H. Kunikata and T. Nakazawa, "Recent clinical applications of laser speckle flowgraphy in eyes with retinal disease," *Asia Pacific Journal of Ophthalmology*, vol. 5, no. 2, pp. 151–158, 2016.

[19] P. J. Dolman and J. Rootman, "VISA classification for Graves orbitopathy," *Ophthalmic Plastic and Reconstructive Surgery*, vol. 22, no. 5, pp. 319–324, 2006.

[20] D. DeMers and D. Wachs, "Physiology, Mean Arterial Pressure," *StatPearls [Internet]*, StatPearls Publishing, Treasure Island (FL), 2019.

[21] M. Sehi, J. G. Flanagan, L. Zeng, R. J. Cook, and G. E. Trope, "Relative change in diurnal mean ocular perfusion pressure: a risk factor for the diagnosis of primary open-angle glaucoma," *Investigative Ophthalmology & Visual Science*, vol. 46, no. 2, pp. 561–567, 2005.

[22] V. G. Likhvantseva, S. I. Kharlap, E. V. Korosteleva et al., "Contribution of hemodynamic disturbances in magistral vessels to optic neuropathy progression and ocular tension changes in endocrine ophthalmopathy," *Vestnik Oftalmologii*, vol. 131, no. 4, pp. 32–37, 2015.

[23] D. Somer, S. B. Ozkan, H. Ozdemir, S. Atilla, M. F. Söylev, and S. Duman, "Colour Doppler imaging of superior ophthalmic vein in thyroid-associated eye disease," *Japanese Journal of Ophthalmology*, vol. 46, no. 3, pp. 341–345, 2002.

[24] M. Jamshidian-Tehrani, S. Nekoozadeh, E. Alami et al., "Color Doppler imaging of orbital vasculature before and after orbital decompression in thyroid eye disease," *Orbit*, vol. 38, no. 3, pp. 173–179, 2019.

[25] P. Saeed, S. Tavakoli Rad, and P. H. L. T. Bisschop, "Dysthyroid optic neuropathy," *Ophthalmic Plastic & Reconstructive Surgery*, vol. 34, no. 4S, pp. S60–S67, 2018.

[26] G. Garhöfer, G. Fuchsjäger-Mayrl, C. Vass, B. Pemp, A. Hommer, and L. Schmetterer, "Retrobulbar blood flow velocities in open angle glaucoma and their association with mean arterial blood pressure," *Investigative Ophthalmology & Visual Science*, vol. 51, no. 12, pp. 6652–6657, 2010.

[27] N. Kiyota, Y. Shiga, N. Takahashi et al., "Progression in open-angle glaucoma with myopic disc and blood flow in the optic nerve head and peripapillary chorioretinal atrophy zone," *Ophthalmology Glaucoma*, vol. 3, no. 3, pp. 202–209, 2020.

[28] T. Sugiyama, M. Araie, C. E. Riva, L. Schmetterer, and S. Orgul, "Use of laser speckle flowgraphy in ocular blood flow research," *Acta Ophthalmologica*, vol. 88, no. 7, pp. 723–729, 2010.

[29] C. D. Noce, A. Vagge, M. Nicolò, and C. E. Traverso, "Evaluation of choroidal thickness and choroidal vascular blood flow in patients with thyroid-associated orbitopathy (TAO) using SD-OCT and Angio-OCT," *Graefes Archive for Clinical and Experimental Ophthalmology*, vol. 258, no. 5, pp. 1103–1107, 2020.

[30] C. Iovino, M. Pellegrini, F. Bernabei et al., "Choroidal vascularity index: an in-depth analysis of this novel optical coherence tomography parameter," *Journal of Clinical Medicine*, vol. 9, no. 2, p. 595, 2020.

[31] N. Aizawa, H. Kunikata, F. Nitta et al., "Age- and sex-dependency of laser speckle flowgraphy measurements of optic nerve vessel microcirculation," *PLoS One*, vol. 11, no. 2, article e0148812, 2016.

[32] T. Iwase, K. Yamamoto, K. Yanagida et al., "Investigation of causes of sex-related differences in ocular blood flow in healthy eyes determined by laser speckle flowgraphy," *Scientific Reports*, vol. 7, no. 1, pp. 13878–13878, 2017.

[33] M.-C. Lin, F.-M. Hsu, Y.-S. Bee, and L.-P. Ger, "Age influences the severity of Graves' ophthalmopathy," *The Kaohsiung Journal of Medical Sciences*, vol. 24, no. 6, pp. 283–288, 2008.

Hindawi
BioMed Research International
Volume 2022, Article ID 4808194, 10 pages
https://doi.org/10.1155/2022/4808194

Research Article

The Changes in Optic Nerve after Orbital Decompression Surgery for Thyroid Eye Disease and Case Reports of Ischemic Optic Neuropathy

Yun Hsia,[1,2] Chia-Chieh Hsiao,[2] Yi-Hsuan Wei ,[2] I-Wen Lai,[2] Chao-Wen Lin,[2,3] and Shu-Lang Liao [2,3]

[1]*National Taiwan University Hospital Jin-Shan Branch, New Taipei City, Taiwan*
[2]*Department of Ophthalmology, National Taiwan University Hospital, Taipei, Taiwan*
[3]*College of Medicine, National Taiwan University, Taipei, Taiwan*

Correspondence should be addressed to Shu-Lang Liao; liaosl89@ntu.edu.tw

Received 10 November 2021; Revised 6 January 2022; Accepted 7 February 2022; Published 27 February 2022

Academic Editor: Chieh-Chih Tsai

Copyright © 2022 Yun Hsia et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Purpose. To demonstrate the changes in the retinal nerve fiber layer (RNFL) after orbital decompression for thyroid eye disease (TED). *Methods.* We retrospectively enrolled 52 surgical TED patients, 30 nonsurgical TED patients, and 30 control subjects. Five surgical TED eyes with disc edema were excluded. The surgical TED patients were classified into the "dysthyroid optic neuropathy (DON)" group (16 eyes) and the "non-DON" group (83 eyes). Optical coherence tomography (OCT) and visual field (VF) examinations were performed preoperatively and 6 months later. The control subjects and nonsurgical TED patients received two OCT examinations at 6-month intervals. The postoperative changes in the RNFL thickness were compared between groups. Three cases with severe postoperative vision loss were presented additionally. *Results.* The changes in the RNFL thickness of the controls ($0.5 \pm 3.4\,\mu$m) and the nonsurgical TED patients ($0.3 \pm 2.8\,\mu$m) were significantly smaller than the surgical TED patients ($P < 0.001$). The DON group ($-9.2 \pm 9.2\,\mu$m) had greater RNFL thickness reduction than the non-DON group ($-3.9 \pm 5.4\,\mu$m) ($P = 0.002$). Bone removal decompression was associated with decreased RNFL in the non-DON ($P = 0.025$; $\beta = -2.49$) and DON ($P = 0.042$; $\beta = -9.43$) groups. Three cases who were hard to operate due to extensive fibrosis experienced severe vision loss postoperatively due to anterior ischemic optic neuropathy, posterior ischemic optic neuropathy, and posterior ciliary artery occlusion, respectively. *Conclusions.* TED patients experienced subclinical optic nerve injury and significant RNFL loss after the orbital decompression surgery. Aggressive manipulation during decompression surgery may lead to dreadful vision loss. Tailored surgical plans and delicate manipulation are warranted.

1. Introduction

Orbital decompression is a well-recognized and effective surgical procedure for thyroid eye disease (TED) [1–3]. It can be performed in inactive TED for disfiguring exophthalmos or in the active phase for dysthyroid optic neuropathy (DON) refractory to medical treatment [2–5]. Different surgical approaches are tailored to the individual patient based on the extent of proptosis, preoperative diplopia, and the presence of DON [3, 4].

Vision loss is a very rare but devastating complication after orbital surgery [6–11]. The prevalence of vision loss after TED decompression surgery ranges from 0.09 to 0.52% [8, 11, 12]. The mechanical injury to the optic nerve or ischemia caused by compression from swelling tissue and hematoma, hypotension during general anesthesia, vasospasm, and arterial occlusion leads to vision loss [11]. In the present study, we reported the clinical manifestations, possible etiologies, and treatment of patients with severe vision loss after orbital decompression surgeries.

The thickness of the retinal nerve fiber layer (RNFL) decreased after orbital decompression surgery in eyes with TED and DON. This could be attributed to the mixture of resolved disc swelling and chronic optic nerve atrophy [13, 14]. However, no study had investigated the RNFL changes in TED eyes without DON. We postulated that orbital decompression surgery per se might cause minor and subclinical injury to the optic nerve. Therefore, we evaluated the changes in parameters of optical coherence tomography (OCT) and visual field (VF) tests in TED patients with and without DON after orbital decompression surgery.

2. Methods

We retrospectively enrolled patients with TED receiving orbital decompression surgery (the surgical TED group) between December 2017 and November 2020 in National Taiwan University Hospital. The diagnosis of TED was based on the consensus of the European Group on Graves' Orbitopathy (EUGOGO) [15]. All patients underwent comprehensive examinations, including the slit-lamp biomicroscopy, the measurement of best-corrected visual acuity (BCVA) and intraocular pressure (CT-80 Non-Contact Computerized Tonometer; Topcon Corp, Tokyo, Japan), Hertel exophthalmometry, color fundus photography, and orbital computerized tomography (CT). Patients with optic neuropathy other than DON, retinal diseases, history of intraocular surgery other than cataract surgery, or ocular trauma were excluded. Patients with disc swelling on indirect ophthalmoscope or color fundus photography were excluded. The diagnosis of DON was made if the patient had decreased visual acuity (logarithm of the minimal angle of resolution [LogMAR] visual acuity > 0.2) due to optic neuropathy and the following presentations: impaired color vision, and/or relative afferent pupillary defect (RAPD), and/or prolonged latency and reduced amplitude of visual evoked potentials test, and/or VF defect, and apical crowding on orbital imaging [16, 17]. The treatment algorithms for the TED were described in our previous publication [4]. The most common surgical indication in the non-DON group is to correct the disfiguring exophthalmos. The surgery would be arranged when the patient had stable thyroid function and inactive TED (clinical activity score [CAS] < 3) for 3-6 months. A seven-item CAS was used, including spontaneous retrobulbar pain, pain on upward or downward gaze, redness of eyelids, redness of conjunctiva, swelling of caruncle or plica, swelling of eyelids, and chemosis. Patients presented with active TED were treated with systemic steroids or other immunosuppressants before the surgery. If the patient had vision-threatening conditions, such as optic neuropathy and exposure keratopathy, the surgery would be arranged after the active inflammation was at least partially controlled by systemic treatments.

Medical charts were retrospectively reviewed, and the relevant data at preoperative evaluation and postoperative 6 months were recorded. TED patients who did not receive orbital decompression (the nonsurgical TED group) and control subjects without optic neuropathy and retinal diseases were enrolled as controls, respectively. Institutional Review Board/Ethics Committee approval was obtained, and the research adhered to the tenets of the Declaration of Helsinki. The informed consent was waived.

2.1. Spectral-Domain OCT. Optic nerve head scanning was performed using spectral-domain OCT (Cirrus HD-OCT 4000, Carl Zeiss Meditec Inc., Dublin, CA, USA). The average RNFL thickness, RNFL thickness at each quadrant, rim area, disc area, cup-to-disc ratio, and cup volume were recorded. Images with signal strength < 7 or motion artifact were excluded. Only patients with OCT taken preoperatively and at postoperative 6 months would be included for analysis. The average RNFL thickness of nonsurgical TED patients and control subjects with two available OCT scans at a 6-month-interval were recorded.

2.2. VF Test. The VF test (Humphrey visual field analyser, Carl Zeiss Meditec, Dublin, CA, USA) was performed using the 24–2 SITA-fast program. Reliable visual field test result was defined as false positive $< 33\%$, false negative $< 33\%$, and fixation loss $< 20\%$. Mean deviation (MD), pattern standard deviation (PSD), and visual field index (VFI) were recorded.

2.3. Statistical Analysis. All statistical analyses were performed using *R* (version 4.0.3; R Foundation for statistical computing, Vienna, Austria). The age and sex between TED patients and controls were compared using the analysis of variance and chi-squared test, respectively. The generalized linear model and generalized estimating equations (GEE) were used to compare the clinical features between TED patients and to compare the clinical features before and after the orbital decompression surgery. To analyze the factors associated with the RNFL changes after the orbital decompression surgery, univariable linear regression with GEE model was performed. Variables with P value <0.1 were included in the multivariable model. P value <0.05 was considered statistically significant.

3. Results

We enrolled 52 patients (104 eyes) in the surgical TED group, 30 patients (60 eyes) in the nonsurgical TED group, and 30 control subjects (60 eyes). Five TED eyes in the surgical group had disc swelling noted on fundus examination and were excluded due to possible interference on OCT interpretation. In the surgical TED group, 16 eyes from 11 patients had DON (the DON group), while 83 eyes from 45 patients were classified into the non-DON group. Table 1 shows the baseline clinical features of TED patients and control subjects. There was no difference in sex and age between TED patients and control subjects. To compare the nonsurgical and surgical TED group, the surgical group had more significant proptosis ($P < 0.001$), higher intraocular pressure ($P < 0.001$), worse MD ($P < 0.001$), and higher CAS ($P < 0.001$). In the surgical TED group, the DON group was older ($P = 0.012$) and had male predominance (82%) ($P = 0.020$). DON patients tended to receive bone removal orbital decompression (BROD) ($P = 0.010$) and had worse visual acuity ($P = 0.005$) and MD ($P < 0.001$). Twenty-five (55.6%) non-DON patients and 6 DON (54.5%) patients received systemic steroid treatment before the surgery, respectively ($P = 0.999$). The number of patients with

Table 1: Baseline demographics and clinical features of patients with thyroid eye disease and controls.

	Between-group comparison				Subgroup analysis: Surgical TED[a]		
	Control	Nonsurgical TED	Surgical TED	P value	Non-DON	DON	P value
Patients (n)	30	30	52		45	11	
Eyes (n)	60	60	99		83	16	
Age (years)	51.7 ± 5.8	56.7 ± 10.2	53.8 ± 10.6	0.057	52.6 ± 10.6	60.1 ± 8.5	**0.012**
Sex (male)	13 (43.3)	9 (30)	23 (43.4)	0.439	17 (37.8)	9 (81.8)	**0.020**
Hertel exophthalmolmetry (mm)		18.2 ± 3.4	22.1 ± 2.3	**<0.001**	22.0 ± 2.2	22.5 ± 3.0	0.560
BROD (%)		NA	49 (49.5)		36 (43.4)	13 (81.3)	**0.010**
FROD (%)		NA	50 (50.5)		47 (56.6)	3 (18.7)	**0.010**
Intraocular pressure (mmHg)		16.3 ± 2.5	22.3 ± 5.4	**<0.001**	21.8 ± 5.2	24.6 ± 6.0	0.130
LogMAR visual acuity		0.05 ± 0.12	0.10 ± 0.23	0.074	0.06 ± 0.11	0.38 ± 0.44	**0.005**
EOM limitation (%)		33 (55)	66 (66.7)	0.220	52 (62.7)	14 (87.5)	0.100
EOM enlargement (%)		47 (78.3)	77 (77.8)	0.987	61 (73.5)	16 (100)	**0.040**
Mean deviation (dB)		−1.24 ± 1.44	−3.74 ± 4.55	**<0.001**	−2.74 ± 3.63	−8.95 ± 5.37	**<0.001**
Abnormal thyroid function (%)		8 (26.7)	20 (37.7)	0.400	16 (35.6)	4 (36.4)	0.999
Preoperative clinical activity score		1 (0-2)	1 (0-7)	**<0.001**	1 (0-7)	2 (0-4)	0.310

[a]Four patients had one eye in the non-DON group and the other eye in the DON group. BROD: bone removal orbital decompression; DON: dysthyroid optic neuropathy; EOM: extraocular muscle; FROD: fat-removal orbital decompression; LogMAR: logarithm of the minimum angle of resolution; NA: not applicable; TED: thyroid eye disease; mean ± standard deviation; median: range; number: percent. Significant P values are shown in bold.

abnormal thyroid function tests was not significantly different between the non-DON and DON groups ($P = 0.999$).

Table 2 demonstrates the comparison of clinical features before and after orbital decompression surgery. After the surgery, proptosis and intraocular pressure decreased significantly in both groups. Both the non-DON ($P < 0.001$) and the DON ($P = 0.003$) group had a significant reduction of average RNFL thickness. The average cup-to-disc ratio and cup volume increased in both groups. The parameters of the VF test did not change in the non-DON group, while the MD and PSD improved in the DON group. Figure 1 shows the changes in average RNFL thickness of the surgical and nonsurgical TED patients and the control subjects. The baseline RNFL thickness was not different between the DON and non-DON groups ($P = 0.200$). The changes in RNFL thickness of the control subjects ($0.5 \pm 3.4\,\mu$m) and the nonsurgical TED patients ($0.3 \pm 2.8\,\mu$m) were significantly smaller than the surgical TED patients ($P < 0.001$ in both DON and non-DON groups). The DON group ($-9.2 \pm 9.2\,\mu$m) had greater RNFL thickness reduction than the non-DON group ($-3.9 \pm 5.4\,\mu$m) ($P = 0.002$).

Table 3 reveals factors associated with the change in RNFL after orbital decompression surgery in the univariable model. In the non-DON group, the multivariable linear regression showed that BROD ($P = 0.025$; $\beta = -2.49$), baseline MD ($P < 0.001$; $\beta = 0.64$), and age ($P = 0.040$; $\beta = -0.12$) were associated with the change in average RNFL thickness after surgery. In the DON group, the multivariable linear regression showed that BROD ($P = 0.042$; $\beta = -9.43$) and the baseline RNFL thickness of nasal quadrant of RNFL ($P = 0.002$; $\beta = -0.54$) were associated with the change in average RNFL thickness after surgery. Receiving BROD was associated with decreased RNFL in both groups.

Despite extremely low prevalence, severe vision loss could occur after orbital decompression surgery for TED. We identified three patients and described the detailed clinical information in the following sections. Their data was not included in the analysis mentioned above.

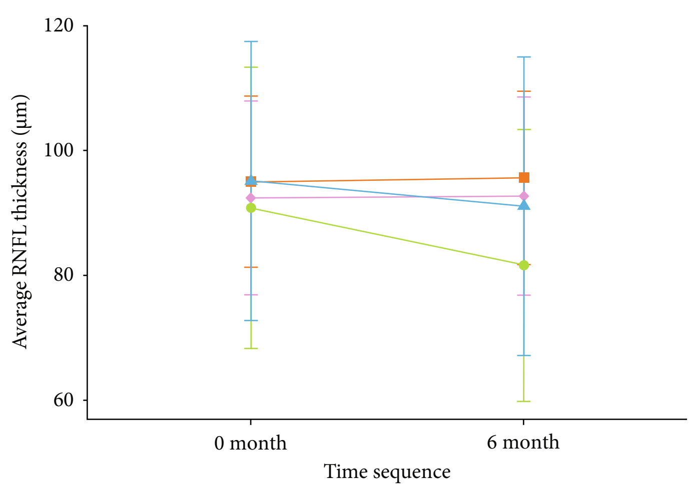
3.1. Case 1. A male patient in his 20s had proptosis with 22 mm for the right eye and 21 mm for the left eye measured by Hertel exophthalmometry. There was no evidence of DON, and his BCVA was 20/20 in both eyes. Subconjunctival FROD was performed, and 5.6 ml and 5.1 ml of orbital fat were removed from his right and left eye, respectively. However, he complained VF defect in the right eye two days after the surgery. Although his BCVA was unchanged, he had a dilated pupil, a positive RAPD sign, and impaired color vision. Indirect ophthalmoscopy showed a pinkish disc with a clear margin. OCT scan showed normal and symmetric RNFL (Figure 2(a)). However, the VF test revealed severe upper defect (MD, -27.17 dB) (Figure 2(b)). Magnetic resonance imaging (MRI) scan showed no intraorbital hematoma or enhancement along the optic nerve. The tentative diagnosis was posterior ischemic optic neuropathy (PION). Intravenous steroid pulse therapy was given for three days (250 mg four times per day). However, the OCT scan showed inferior RNFL loss (Figure 2(c)), the right optic disc became pallor (Figure 2(d)), and his BCVA declined to 20/25 three months later.

3.2. Case 2. A female patient in her 40s had proptosis with 20 mm for the right eye and 22 mm for the left eye. There was no evidence of DON, and her BCVA was 20/30 in both eyes. Subconjunctival FROD was performed, and 4.2 ml and 5.5 ml of orbital fat were removed from her right and left

Table 2: Clinical characteristics before and after orbital decompression surgery.

	Non-DON (83 eyes)			DON (16 eyes)		
	Preoperative	Postoperative	*P* value	Preoperative	Postoperative	*P* value
Average RNFL (μm)	95.1 ± 11.4	91.1 ± 12.2	**<0.001**	90.8 ± 11.5	81.6 ± 11.1	**0.003**
Rim area (mm^2)	1.20 ± 0.28	1.18 ± 0.32	0.170	1.16 ± 0.25	0.99 ± 0.20	**<0.001**
Average cup-to-disc ratio	0.56 ± 0.15	0.60 ± 0.15	**0.002**	0.53 ± 0.19	0.62 ± 0.12	**0.008**
Vertical cup-to disc ratio	0.52 ± 0.16	0.56 ± 0.16	**0.002**	0.48 ± 0.20	0.57 ± 0.16	0.110
Cup volume (mm^3)	0.246 ± 0.227	0.280 ± 0.243	**<0.001**	0.215 ± 0.209	0.268 ± 0.225	**<0.001**
RNFL of superior quadrant (μm)	115.0 ± 19.4	109.0 ± 22.1	**<0.001**	110.1 ± 22.4	97.4 ± 19.5	**0.001**
RNFL of temporal quadrant (μm)	80.6 ± 15.5	78.7 ± 16.1	0.170	74.4 ± 13.0	65.8 ± 14.7	**0.018**
RNFL of inferior quadrant (μm)	117.0 ± 22.1	110.0 ± 22.1	**<0.001**	108.8 ± 19.7	100.4 ± 20.4	**0.003**
RNFL of nasal quadrant (μm)	67.5 ± 12.2	66.0 ± 12.5	**0.009**	70.2 ± 11.7	66.7 ± 8.6	0.100
Mean deviation (dB)	−2.74 ± 3.63	−2.38 ± 3.82	0.160	−8.95 ± 5.37	−5.25 ± 4.46	**0.047**
Pattern standard deviation (dB)	2.56 ± 2.32	2.42 ± 2.37	0.510	5.42 ± 3.37	2.97 ± 2.19	**0.016**
Visual field index (%)	95.3 ± 8.2	95.1 ± 9.7	0.800	80.6 ± 13.7	90.8 ± 13.8	0.058
Hertel exophthalmometry (mm)	22.0 ± 2.2	17.4 ± 1.7	**<0.001**	22.5 ± 3.0	17.7 ± 2.5	**<0.001**
LogMAR visual acuity	0.06 ± 0.11	0.07 ± 0.15	0.450	0.38 ± 0.44	0.26 ± 0.42	0.053
Intraocular pressure (mmHg)	21.8 ± 5.2	17.1 ± 3.0	**<0.001**	24.6 ± 6.0	16.7 ± 4.0	**<0.001**

DON: dysthyroid optic neuropathy; EOM: extraocular muscle; LogMAR: logarithm of the minimum angle of resolution; TED: thyroid eye disease. Significant *P* values are shown in bold.



Group	RNFL	RNFL	P-value	RNFL difference
Control (60)	95.0 ± 7.0	95.6 ± 7.1	0.750	0.5 ± 3.4
Non-surgical TED (60)	92.4 ± 7.9	92.7 ± 8.1	0.890	0.3 ± 2.8
Surgical TED (Non-DON) (83)	95.1 ± 11.4	91.1 ± 12.2	<0.001	−3.9 ± 5.4
Surgical TED (DON) (16)	90.8 ± 11.5	81.6 ± 11.1	0.003	−9.2 ± 9.2

Figure 1: The changes in the thickness of the retinal nerve fiber layer (RNFL) of patients with thyroid eye disease (TED) and healthy controls. There is no significant difference in RNFL thickness between the four groups at baseline. Surgical TED patients have a significant RNFL loss after the orbital decompression surgery, while the control subjects and nonsurgical TED patients do not have RNFL changes between two examinations of the optical coherence tomography.

eye, respectively. However, prominent hemorrhagic chemosis, extraocular muscle movement limitation in horizontal gaze, positive RAPD sign, and decreased vision to finger counting in the left eye were noted on postoperative day 1. Indirect ophthalmoscopy showed marked disc swelling (Figure 3(a)). Fluorescein angiography demonstrated disc leakage (Figure 3(b)). Orbital CT scan revealed some hematoma in the left orbit without optic nerve compression. The tentative diagnosis was anterior ischemic optic neuropathy (AION). Emergent hematoma evacuation was performed

Table 3: The univariable analysis of factors associated with RNFL deterioration after decompression.

	Non-DON		DON	
	β-Coefficients (95% CI)	P value	β-Coefficients (95% CI)	P value
Age (years)	-0.15 (-0.29–-0.01)	**0.035**	-0.04 (-0.57–0.50)	0.898
Male sex	-1.68 (-4.75–1.40)	0.285	6.57 (0.71–12.40)	**0.028**
Intraocular pressure (mmHg)	0.04 (-0.13–0.20)	0.646	0.22 (-0.54–0.98)	0.563
LogMAR visual acuity	-13.0 (-23.00–-3.04)	**0.011**	-3.22 (-11.60–5.13)	0.450
Mean deviation (dB)	0.58 (0.29–0.87)	**<0.001**	-0.01 (-0.72–0.71)	0.989
Average RNFL (μm)	-0.09 (-0.24–0.06)	0.222	-0.58 (-0.87–-0.29)	**<0.001**
RNFL of superior quadrant (μm)	-0.02 (-0.09–0.05)	0.506	-0.17 (-0.31–0.03)	**0.014**
RNFL of temporal quadrant (μm)	-0.05 (-0.12–0.02)	0.168	-0.27 (-0.67–0.13)	0.186
RNFL of inferior quadrant (μm)	-0.03 (-0.11–0.05)	0.474	-0.18 (-0.38–0.03)	0.089
RNFL of nasal quadrant (μm)	-0.07 (-0.16–0.03)	0.167	-0.51 (-0.77–-0.25)	**<0.001**
Hertel exophthalmometry (mm)	0.05 (-0.48–0.59)	0.855	4.82 (2.28–7.36)	**<0.001**
BROD	-2.48 (-4.79–-0.18)	**0.035**	-7.95 (-15.40–-0.54)	**0.036**
Diplopia	1.36 (-1.41–4.13)	0.336	4.90 (-5.30–15.10)	0.347
EOM enlargement	-0.93 (-3.36–1.50)	0.453	Not available*	Not available*
Clinical activity score	0.20 (-0.78–1.17)	0.690	4.35 (2.85–5.85)	**<0.001**
Systemic steroid treatment	-2.12 (-4.78–0.53)	0.117	10.3 (3.61–17.00)	**<0.001**

BROD: bone removal orbital decompression; DON: dysthyroid optic neuropathy; LogMAR: logarithm of the minimum angle of resolution. The value of change in RNFL equals the postoperative average RNFL thickness minus the preoperative average RNFL thickness. *The results are not available since all patients in the DON group had EOM enlargement. Significant P values are shown in bold.

due to rapid worsening of visual acuity to hand motion. Intravenous steroid pulse therapy (250 mg four times per day) was given for three days. Unfortunately, the visual improvement was limited, and her BCVA was only finger counting at 10 cm 6 months later. The disc became pallor, and the OCT scan showed diffuse RNFL loss. The visual field defect was significant (Figures 3(c)–3(e)).

3.3. Case 3. A female patient in her 50s had proptosis with 21.5 mm for both eyes. There was no evidence of DON, and her BCVA was 20/20 in both eyes. Subconjunctival FROD was performed, and 5 ml and 4.8 ml of orbital fat were removed from her right and left eye, respectively. However, on postoperative day 1, she reported decreased visual acuity (20/30) and VF defect. On examinations, there were a mild RAPD sign, decreased color vision, and inferior optic disc swelling in the left eye (Figure 4(a)). The VF test showed superior defect, and the MD was -25.06 dB (Figure 4(b)). Emergent orbital CT scan and MRI showed no intraorbital hematoma, optic nerve avulsion, or definite optic neuropathy. Two days after the operation, the vision suddenly decreased to hand motion at 50 cm. Indirect ophthalmoscopy showed marked optic disc swelling. Color fundus photography showed triangular, well-defined, patchy infarcts lying deep to the retina. Fluorescence angiography revealed delayed choroidal perfusion and late staining of the patchy lesions in the left eye (Figures 4(c)–4(e)). The tentative diagnosis was posterior ciliary artery occlusion. Intravenous pulse steroid therapy (250 mg four times per day), subcutaneous enoxaparin (30 mg twice per day), and oral ginkgocentrate and mecobalamin were given for five days. Despite the prompt management, the left eye had no light perception three days later.

4. Discussion

Orbital decompression surgery had a close approximation to numerous neurovascular structures. Damage to those structures could lead to devastating complications. We found that RNFL thickness decreased significantly in TED patients after orbital decompression surgery. In contrast, TED patients who did not receive orbital decompression had no decline in RNFL thickness. Patients with DON had a more dramatic decrease in RNFL thickness, which may be associated with the additional effect of resolving disc edema or chronic optic nerve atrophy. Moreover, patients who received BROD were more susceptible to RNFL loss than those receiving FROD. However, the RNFL change after orbital decompression surgery did not cause functional deterioration. Despite the extremely low prevalence of postoperative vision loss, we identified three patients who suffered from significant vision loss after orbital decompression surgery due to AION, PION, and posterior ciliary artery occlusion, respectively.

In the present study, we would like to know whether the orbital decompression surgery may damage the optic nerve. The RNFL thickness varies significantly between TED patients with different severities [18]. Patients with mild TED had comparable RNFL thickness to controls, while those with moderate-to-severe TED have lower value of RNFL thickness due to subclinical optic nerve damage [18]. Orbital tissue swelling and elevated intraorbital pressure may lead to hypoxia and ischemia of the optic nerve

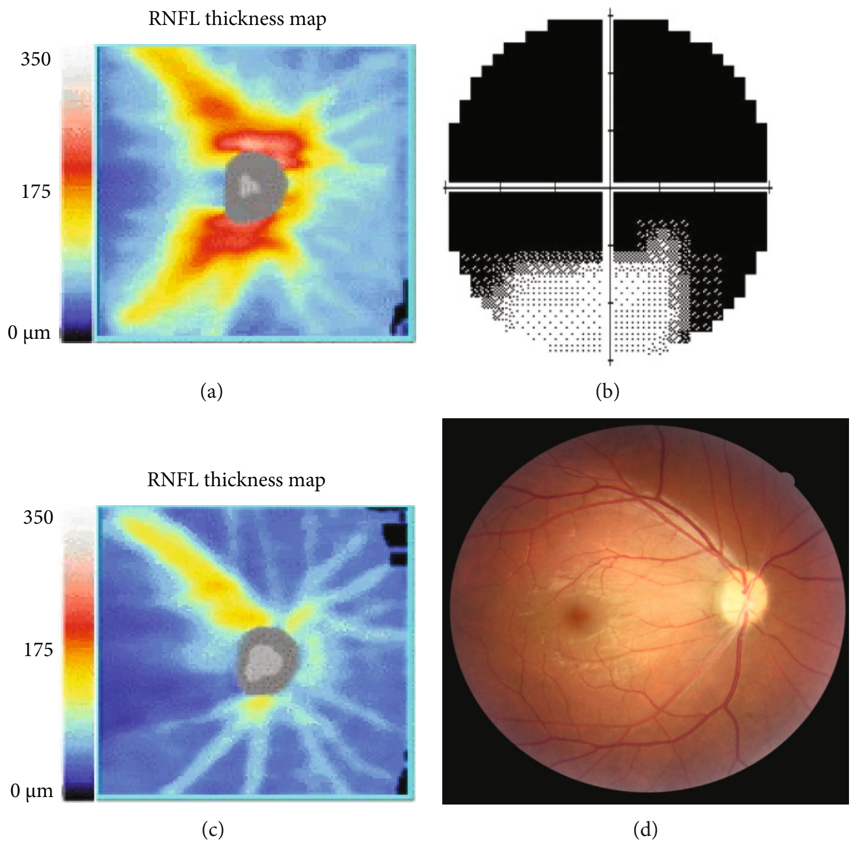


FIGURE 2: Clinical presentations of a patient with thyroid eye disease experience severe vision loss after the decompression surgery (case 1). The patient reports visual field defect after an uneventful fat-removal orbital decompression. (a) Initially, the optical coherence tomography scan shows intact retinal nerve fiber layer (RNFL), and the average thickness is 96 μm. (b) However, the visual field test shows upper visual field defect with the mean deviation -27.17 dB. (c) Diffuse loss of inferior RNFL is noted, and the average thickness is 61 μm three months after the surgery. (d) Color fundus photography reveals that the optic disc becomes pallor. The clinical presentations are compatible with posterior ischemic optic neuropathy.

head. This was supported by the fact that peripapillary vessel density was lower in eyes with active TED [19, 20]. Patients with acute DON had increased RNFL thickness due to disrupted axoplasmic flow and optic disc swelling [20], while patients with chronic DON had thinner RNFL due to optic nerve atrophy [21]. Therefore, we classified TED patients into the DON and the non-DON groups to clarify the changes of RNFL thickness after orbital decompression surgery.

We found that the baseline RNFL thickness in both DON and non-DON groups was comparable to the control subjects. The RNFL thickness in the DON group may reflect the mixed effects of disc swelling and optic nerve damage, while there was no evidence of structural change in the non-DON group. In order to eliminate the possible test-retest variability of OCT scans, we compared the RNFL changes of the TED eyes to the two measurements of control subjects separated by six months. After the surgery, TED eyes had a significant RNFL deterioration compared to the controls. The DON and non-DON groups had a 9 and 4 μm RNFL decrease, respectively. A decrease of RNFL thickness by 4 μm measured with Cirrus OCT should be considered a true deterioration [22, 23]. In order to clarify the possibility of RNFL deterioration due to the disease nature of TED, we compared the surgical TED patients to the TED patients who did not receive orbital decompression. The nonsurgical TED patients did not show significant RNFL deterioration during the follow-up. Since the nonsurgical TED patients did not need surgical intervention, it was reasonable that they had less significant proptosis, lower intraocular pressure, and CAS than the patients in the surgical TED group. However, the proptosis was corrected, and intraocular pressure decreased immediately after the orbital decompression. Therefore, the postoperative RNFL loss in the surgical TED group may be mainly attributed to the surgical traction to the optic nerve and its supplying blood vessels and the compression from postoperative tissue swelling. The resolving disc edema and chronic optic nerve atrophy may explain that the DON group had more RNFL loss [13, 14]. However, the role of resolving disc edema is less critical in our cohort since we excluded cases with disc swelling. The vulnerable optic nerve in the DON group may be more susceptible to the RNFL loss related to decompression surgery. Moreover, we found that BROD was associated with a more significant decrease in RNFL thickness than the FROD in both DON and non-DON groups. BROD had a higher complication rate due to the alteration of normal orbit anatomy

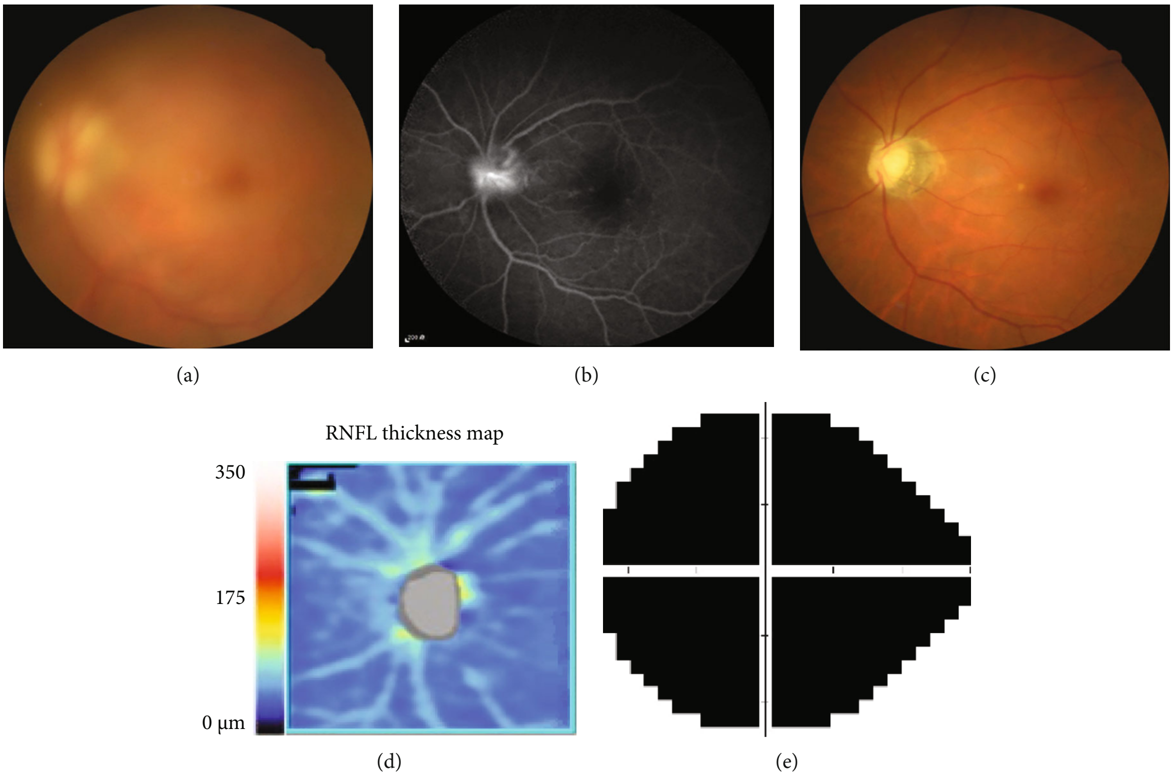


Figure 3: Clinical presentations of a patient with thyroid eye disease experience severe vision loss after the decompression surgery (case 2). The patient reports decreased vision to number of digits after an uneventful fat-removal orbital decompression. (a) Color fundus photography shows significant disc edema. The image is blurry due to corneal edema. (b) Fluorescein angiography shows disc leakage. The clinical presentations are compatible with anterior ischemic optic neuropathy. (c) Despite the prompt treatment, the optic disc becomes pallor. (d) The optical coherence tomography scan shows diffuse retinal nerve fiber layer loss, and the average thickness was 54 μm. (e) The mean deviation of visual field test is -33.34 dB.

[1, 24]. In the non-DON group, older patients and those with preoperative VF defects had a smaller neuronal reserve and were more vulnerable to the damage associated with decompression surgery. Worth to be mentioned, the systemic steroid treatment before the orbital decompression was associated with less RNFL deterioration in the DON group. It might be possible that those who did not take steroids still had subclinical optic nerve swelling. Therefore, they exhibited more significant RNFL reduction after the operation due to the mixed effect of the resolution of edema and true RNFL loss. However, this association became nonsignificant in the multivariable regression analysis.

Vision loss had been reported as a rare complication after various orbital surgeries, including tumor excision, posttraumatic reconstruction, and decompression for TED [9, 11]. Among these orbital surgeries, orbital decompression for TED had the lowest risk of vision loss [9, 11]. One patient receiving endoscopic BROD had vision loss caused by ischemic optic neuropathy one week later [7]. Other studies regarding the outcomes of orbital decompression surgery also reported very few cases with postoperative vision loss [8, 12, 25]. The possible etiologies of vision loss included surgical manipulation, thermal and electrical injury, compression from bony fragments, vasospasm due to inflammation, and elevated intraorbital pressure due to tissue swelling, retrobulbar hemorrhage, and tight pressure patching [10, 11]. Ischemic events included AION, PION, posterior ciliary artery occlusion, central retinal artery occlusion, or ophthalmic artery occlusion could occur [10, 11].

In the present study, three cases with severe vision loss after FROD had different underlying etiologies. The first patient had an episode of PION. Hypotension during general anesthesia [26] was not noted. The surgical traction may damage the pial plexus directly or cause vasospasm and compromise the blood supply of the intraorbital optic nerve [11]. Marked tissue swelling may also increase intraorbital pressure and reduce blood perfusion. Since we removed the inferior orbital fat and possibly damaged the inferior portion of optic nerve, the patient had a corresponding superior VF defect. The optic disc appeared normal at the acute phase but became pallor 4-6 weeks later [26]. The second patient had AION. Although peribulbar hematoma was identified on imaging, there was no evidence of direct compression on the optic nerve. The increased intraorbital pressure and the postoperative inflammation may contribute to the optic nerve head ischemia. Emergent surgical evacuation of hematoma had a limited effect on the visual prognosis of this case. The third patient had marked and progressive disc swelling. Moreover, delayed choroidal perfusion and ischemia of the outer retina were noted on fluorescein

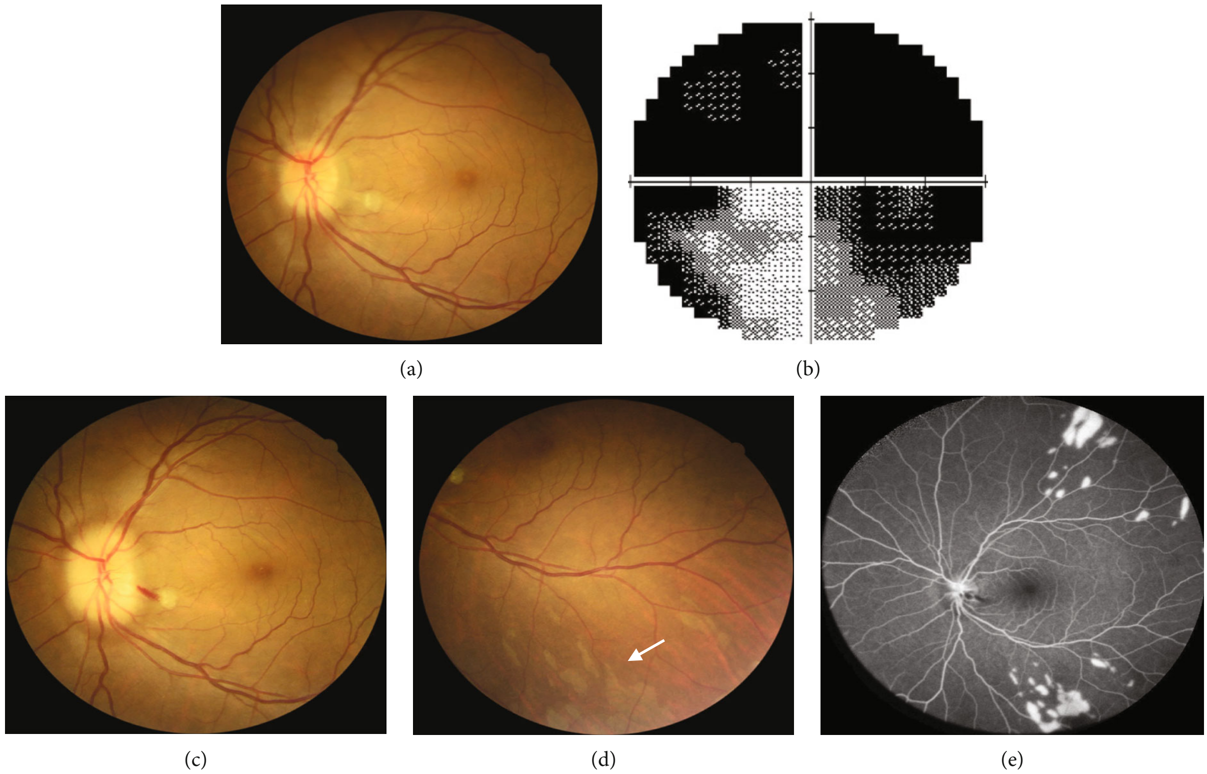


FIGURE 4: Clinical presentations of a patient with thyroid eye disease experience severe vision loss after the decompression surgery (case 3). The third patient reports progressive loss of vision after an uneventful fat-removal orbital decompression. (a) Initially, color fundus photography showed disc edema. (b) Visual field test shows a superior defect, and the mean deviation is -25.06 dB. Two days later, the vision decreases to the hand motion level. (c) Color fundus photography shows the progression of disc edema. There are also a cotton-wool spot and disc hemorrhage. (d) There are also some triangular, well-defined, patchy choroidal ischemic lesions (arrow). (e) Fluorescein angiography reveals marked delayed choroidal perfusion and late staining of the patchy lesions. The clinical presentations are compatible with posterior ciliary artery occlusion.

angiography. Infarction of the short posterior ciliary artery led to ischemia of the optic nerve head, choroid, and outer retina [27]. Acute choroidal ischemic lesions are localized and discrete whitish patches and distribute along the territory of the occluded branch of short posterior ciliary artery. Later, they evolve into depigmented lesions [27]. This patient ended up with no light perception due to extensive ischemia. Intravenous steroid pulse therapy had been given in these cases but did not enhance the visual improvement. Subcutaneous enoxaparin injection had been advocated in cases with posterior ciliary artery occlusion due to filler injection [28]; however, the effect was also insubstantial in our patient. All these three patients were relatively hard to operate due to extensive fibrosis and adhesion. Aggressive surgical manipulations may predispose to these complications. Therefore, a more conservative surgical plan should be adopted in cases with limited surgical fields to avoid dreadful vision loss.

This study had several limitations. Since we aimed to eliminate the effect of resolving disc edema on postoperative RNFL change, we excluded patients with disc edema. Therefore, the number of DON patients was small, and the data may be less representative for this population. Patients who had ocular hypertension tended to have OCT scans more frequently and were more likely to be included. However, we excluded patients with glaucomatous optic neuropathy, and the intraocular pressure decreased significantly after orbital decompression. Therefore, the intraocular pressure was unlikely to cause the RNFL loss. Additionally, we only observed the RNFL changes 6 months after the surgery. Longer follow-up was necessary to decide whether this RNFL deterioration was an isolated event related to orbital decompression surgery or was progressive due to the chronic optic nerve atrophy. Lastly, different types of orbital decompression, such as medial or lateral wall decompression or other orbital surgeries, including orbital fracture repair and orbital tumor excision, may have different effects on the RNFL. More comprehensive analysis is needed to clarify the impact on RNFL caused by a specific type of orbital surgery.

In conclusion, we found that TED patients had a significant RNFL decrease after the orbital decompression surgery, especially those with DON. BROD was associated with a greater RNFL decrease than FROD. Additionally, we reported three cases with severe vision loss after FROD for TED, presented as AION, PION, and posterior ciliary artery occlusion, respectively. Aggressive surgical manipulation due to extensive adhesion and fibrosis may lead to the complications. Therefore, staying mindful of potential complications and optic nerve damage is imperative. Tailored surgical plan, delicate intraoperative manipulation, and appropriate postoperative follow-up are warranted in TED patients receiving orbital decompression surgery.

Data Availability

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical and privacy concerns.

Conflicts of Interest

No conflicting relationship exists for any author.

References

[1] A. M. Cheng, Y. H. Wei, S. Tighe, H. Sheha, and S. L. Liao, "Long-term outcomes of orbital fat decompression in Graves' orbitopathy," *The British Journal of Ophthalmology*, vol. 102, no. 1, pp. 69–73, 2018.

[2] M. P. Mourits, H. Bijl, M. A. Altea et al., "Outcome of orbital decompression for disfiguring proptosis in patients with Graves' orbitopathy using various surgical procedures," *The British Journal of Ophthalmology*, vol. 93, no. 11, pp. 1518–1523, 2009.

[3] D. B. Rootman, "Orbital decompression for thyroid eye disease," *Survey of Ophthalmology*, vol. 63, no. 1, pp. 86–104, 2018.

[4] A. Cheng, Y.-H. Wei, and S.-L. Liao, "Strategies in surgical decompression for thyroid eye disease," *Oxidative Medicine and Cellular Longevity*, vol. 2020, Article ID 3537675, 2020.

[5] C. H. Wu, T. C. Chang, and S. L. Liao, "Results and predictability of fat-removal orbital decompression for disfiguring graves exophthalmos in an Asian patient population," *American Journal of Ophthalmology*, vol. 145, no. 4, pp. 755–759, 2008.

[6] G. Bonavolontà, "Postoperative blindness following orbital surgery," *Orbit*, vol. 24, no. 3, pp. 195–200, 2005.

[7] A. Asorey-García, R. Martínez-Chico, E. Santos-Bueso, and J. García-Feijoo, "Optic neuropathy after orbital decompression surgery," *Neurología*, vol. 31, no. 1, pp. 62–64, 2016.

[8] S. C. Leong and P. S. White, "Outcomes following surgical decompression for dysthyroid orbitopathy (Graves' disease)," *Current Opinion in Otolaryngology & Head and Neck Surgery*, vol. 18, no. 1, pp. 37–43, 2010.

[9] G. E. Rose, "The "devil's touch"; visual loss and orbital surgery. A synopsis of the Mustardé Lecture, 2006," *Orbit*, vol. 26, no. 3, pp. 147–158, 2007.

[10] J. C. Dohlman and M. K. Yoon, "Principles of protection of the eye and vision in orbital surgery," *Journal of Neurological Surgery Part B: Skull Base*, vol. 81, no. 4, pp. 381–384, 2020.

[11] P. Kansakar and G. Sundar, "Vision loss associated with orbital surgery - a major review," *Orbit*, vol. 39, no. 3, pp. 197–208, 2020.

[12] S. Sellari-Franceschini, I. Dallan, A. Bajraktari et al., "Surgical complications in orbital decompression for Graves' orbitopathy," *Acta Otorhinolaryngologica Italica*, vol. 36, no. 4, pp. 265–274, 2016.

[13] S. Cheng, Y. Yu, Y. You et al., "Retinal nerve fiber layer thickness measured by optical coherence tomography predicts visual recovery after orbital decompression for dysthyroid optic neuropathy," *International Ophthalmology*, vol. 41, no. 9, pp. 3121–3133, 2021.

[14] K. A. Park, Y. D. Kim, and K. I. Woo, "Changes in optical coherence tomography measurements after orbital wall decompression in dysthyroid optic neuropathy," *Eye*, vol. 32, no. 6, pp. 1123–1129, 2018.

[15] L. Bartalena, L. Baldeschi, A. J. Dickinson et al., "Consensus statement of the European group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy," *Thyroid*, vol. 18, no. 3, pp. 333–346, 2008.

[16] A. D. Blandford, D. Zhang, R. V. Chundury, and J. D. Perry, "Dysthyroid optic neuropathy: update on pathogenesis, diagnosis, and management," *Expert Review of Ophthalmology*, vol. 12, no. 2, pp. 111–121, 2017.

[17] Y. H. Wei, M. C. Chi, and S. L. Liao, "Predictability of visual function and nerve fiber layer thickness by cross- sectional areas of extraocular muscles in Graves ophthalmopathy," *American Journal of Ophthalmology*, vol. 151, no. 5, pp. 901–906.e1, 2011.

[18] J. Guo, X. Li, R. Ma, L. Gan, and J. Qian, "The changes of retinal nerve fibre layer and ganglion cell layer with different severity of thyroid eye disease," *Eye*, vol. 36, no. 1, pp. 129–134, 2022.

[19] T. Zhang, W. Xiao, H. Ye, R. Chen, Y. Mao, and H. Yang, "Peripapillary and macular vessel density in dysthyroid optic neuropathy: an optical coherence tomography angiography study," *Investigative Ophthalmology & Visual Science*, vol. 60, no. 6, pp. 1863–1869, 2019.

[20] T. V. Dave, S. Laghmisetty, G. Krishnamurthy et al., "Retinal vascularity, nerve fiber, and ganglion cell layer thickness in thyroid eye disease on optical coherence tomography angiography," *Orbit*, pp. 1–8, 2020.

[21] K.-A. Park, Y.-D. Kim, K. I. Woo, C. Kee, and J. C. Han, "Optical coherence tomography measurements in compressive optic neuropathy associated with dysthyroid orbitopathy," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 254, no. 8, pp. 1617–1624, 2016.

[22] J. C. Mwanza, R. T. Chang, D. L. Budenz et al., "Reproducibility of peripapillary retinal nerve fiber layer thickness and optic nerve head parameters measured with cirrus HD-OCT in glaucomatous eyes," *Investigative Ophthalmology & Visual Science*, vol. 51, no. 11, pp. 5724–5730, 2010.

[23] M. Wadhwani, S. J. Bali, R. Satyapal et al., "Test-retest variability of retinal nerve fiber layer thickness and macular ganglion cell-inner plexiform layer thickness measurements using spectral-domain optical coherence tomography," *Journal of Glaucoma*, vol. 24, no. 5, pp. e109–e115, 2015.

[24] E. Al-Sharif and A. H. Alsuhaibani, "Fat-removal orbital decompression for thyroid associated orbitopathy: the right procedure for the right patient," *Saudi Journal of Ophthalmology*, vol. 31, no. 3, pp. 156–161, 2017.

[25] J. A. Garrity, V. Fatourechi, E. J. Bergstralh et al., "Results of transantral orbital decompression in 428 patients with severe Graves' ophthalmopathy," *American Journal of Ophthalmology*, vol. 116, no. 5, pp. 533–547, 1993.

[26] S. S. Hayreh, "Posterior ischaemic optic neuropathy: clinical features, pathogenesis, and management," *Eye*, vol. 18, no. 11, pp. 1188–1206, 2004.

[27] S. S. Hayreh, "Posterior ciliary artery circulation in health and disease the Weisenfeld lecture," *Investigative Ophthalmology & Visual Science*, vol. 45, no. 3, pp. 749–757, 2004.

[28] G. J. Goodman, M. R. Magnusson, P. Callan et al., "A consensus on minimizing the risk of hyaluronic acid embolic visual loss and suggestions for immediate bedside management," *Aesthetic Surgery Journal*, vol. 40, no. 9, pp. 1009–1021, 2020.