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Assessment of pupillary light reflex using dynamic pupillometry in laser-treated eyes with retinal vein occlusion

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Abstract

Purpose: This study aims to evaluate the pupillary light reflex measured with dynamic pupillometry in patients who underwent retinal laser photocoagulation due to unilateral retinal vein occlusion (RVO).

Methods: A total of 48 patients with unilateral RVO were included in the study. Thirty-four patients had undergone retinal laser photocoagulation while the remaining 14 patients that did not undergo laser treatment were observed for control purposes. Of the laser-treated eyes, 14 eyes (41.2%) had central RVO (CRVO) and 20 eyes (58.8%) had branch RVO (BRVO). Among the 14 patients with RVO without laser treatment, nine eyes (64.3%) had CRVO and five eyes (35.7%) had BRVO. Pupillary light reflexes were assessed with dynamic pupillometry (MonPackOne®; Metrovision, France). The parameters of the eyes with RVO were compared with that of fellow healthy eyes.

Results: Mean patient age was 65.8 ± 10.4 years and median time after photocoagulation was 25.5 months. Eyes that received laser photocoagulation had lower pupil contraction amplitude ($p = 0.037$), prolonged contraction latency ($p = 0.027$), slower contraction velocity ($p = 0.043$), and slower dilation velocity ($p < 0.001$) compared to healthy fellow eyes. Subgroup analysis revealed that eyes with CRVO had lower contraction amplitude ($p = 0.013$) and slower dilation velocity ($p = 0.003$), and eyes with BRVO had slower dilation velocity ($p = 0.003$). Non-laser-treated eyes with RVO revealed no significant difference in any of the pupillary light reflex parameters compared to fellow eyes.

Conclusion: Laser-treated eyes with RVO demonstrated changes in pupillary light reflex parameters including reduced contraction amplitude, prolonged contraction latency, and slower contraction and dilation velocities measured with dynamic pupillometry.

Keywords

Branch retinal vein occlusion, central retinal vein occlusion, dynamic pupillometry, laser photocoagulation, pupillary light reflex

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Introduction

Retinal vein occlusion is the most common retinal vascular disorder after diabetic retinopathy.[1] There are two main anatomical forms of retinal vein occlusions, central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). Retinal vein occlusions are classified as ischemic and non-ischemic according to fluorescein angiography findings.[2]

Retinal vein occlusion is characterized by capillary nonperfusion, and absence of blood and oxygen flow,

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leading to retinal ischemia. Ischemic hypoxia results in neovascularization and edema formation by activating the production of cytokines such as vascular endothelial growth factor. Laser photocoagulation treatment destroys a portion of photoreceptors and reduces oxygen consumption of the retina, establishing a balance between oxygen supply and demand. Laser photocoagulation treatment in RVO is performed to reduce macular edema and prevent neovascularization caused by ischemia. Prophylactic laser photocoagulation treatment in RVO has been shown to reduce the development of neovascularization as well as improve visual acuity.[3]

Animal studies have demonstrated morphological changes in short posterior ciliary nerves depending on the intensity of laser treatment applied to the retina and the proximity of laser spots to ciliary nerves.[4] In humans, cases of accommodation loss and mydriasis following laser photocoagulation treatment have been reported.[5–7] However, there is lack of evidence in the literature regarding the effect of retinal laser treatment on pupillary light responses in patients with retinal vein occlusion. Quantitative measurement of the pupillary light reflex might reveal the existence and degree of ciliary nerve damage occurred during laser photocoagulation.

With the introduction of automated infrared pupillometry devices, objective and quantitative measurement of the pupil diameters and the kinetic responses of the pupil against light stimulation have become possible. Dynamic pupillometry is widely used especially in the evaluation of autonomic dysfunctions.[8–10] This study aims to evaluate the pupillary light reflex responses recorded with an infrared dynamic pupillometry device in eyes with retinal vein occlusion that underwent laser photocoagulation.

Methods

A total of 48 patients with unilateral RVO and no pathology in the fellow eye were included in this cross-sectional comparative study conducted at a tertiary referral university hospital. Thirty-four patients had received laser photocoagulation while 14 patients that did not undergo laser treatment were evaluated for control purposes. The study was approved by the local ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent form was obtained from all patients after they were informed in detail about the course and possible results of the study.

Age, gender, time of diagnosis, and clinical history regarding laser treatment of all patients were assessed. Detailed ophthalmologic examination including visual acuity assessment, intraocular pressure measurement, anterior segment examination with biomicroscope, and dilated fundus examination were conducted on all patients. Fundus fluorescein angiographic (FFA) findings prior to treatment and argon laser treatment parameters including number of laser spots, power, and spot size of patients who underwent retinal laser photocoagulation were reviewed from records. Retinal laser photocoagulation treatment was performed in eyes having more than seven disc diameters of ischemia in FFA and was completed in 4–5 sessions in eyes with CRVO and 1–2 sessions in eyes with BRVO. Laser treatment was applied with the following settings; laser power 200–500 mW, spot size 0.2 mm and pulse duration 0.2 s. The entire circumference of the retina beyond two disc diameters distance from the vascular arcades was treated in eyes with CRVO, and the affected ischemic regions were treated in eyes with BRVO. Exclusion criteria included previous ocular trauma, ocular surgery (aside from intravitreal injections), glaucoma, diabetes mellitus, and other systemic diseases (aside from controlled hypertension).

Pupillary light reflex responses were measured with an infrared dynamic pupillometry device (MonPackOne®; Metrovision, France), which utilizes infrared illumination (880 nm) and a high-resolution infrared imaging sensor that allows the measurement of pupil parameters in full darkness. In a fully dark environment, pupillary responses to white light stimulus (light intensity 100 cd/m^2, on/off time 200/3300 ms) projected to the eye were recorded with the device's infrared camera (measurement sensitivity 0.1 mm). After 5 min of dark adaptation prior to taking measurements, one eye was closed and the responses from the other eye were evaluated. Eight parameters were measured, including initial pupil diameter, contraction amplitude, contraction latency, contraction time, contraction velocity, dilation latency, dilation time, and dilation velocity, and these parameters were compared between eyes with RVO and fellow healthy eyes (Figure 1).

Statistical analysis of the data was performed with SPSS 21.0 (SPSS for Windows, Chicago, USA) package program. Shapiro-Wilk test was used to evaluate the normality distribution of continuous numerical data. The Pearson χ^2 test was used to compare the categorical parameters. Paired samples *t*-test was used for the statistical analysis of parametric data, while Wilcoxon signed-rank test was used to analyze non-parametric data. The correlations between pupillary light reflex parameters and the number of laser spots applied to the retina were measured using Spearman's correlation coefficient. For all evaluations, a p value of less than 0.05 was considered statistically significant.

Results

The main demographic and clinical characteristics of the study participants are given in Table 1. The mean ± SD age of the laser-treated patients was 65.8 ± 10.4 years, and the median (IQR) time elapsed from the completion of laser photocoagulation was 25.5 (4.3–54.0) months. Of the total 34 laser-treated patients, 14 cases were diagnosed with

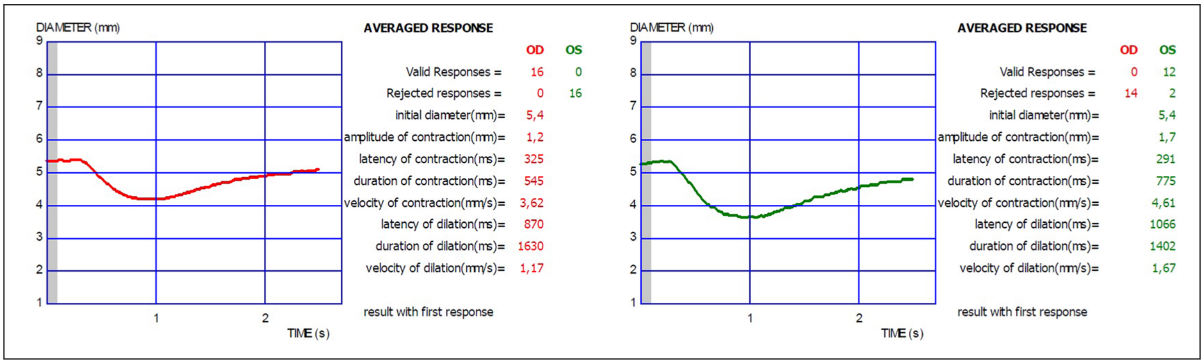

Figure 1. Pupillary light reflex responses measured with infrared dynamic pupillometry in a patient who underwent panretinal laser photocoagulation in the right eye due to central retinal vein occlusion.

Table 1. The main demographic and clinical characteristics of the patients with retinal vein occlusion.

	Patients with CRVO (n = 14)	Patients with BRVO (n = 20)	Patients with RVO without laser treatment (n = 14)
Age (years, mean ± SD)	66.9 ± 13.4	65.1 ± 8.1	59.3 ± 14.1
Sex (F/M)	7/7	10/10	4/10
Total number of laser spots (n, median (IQR))	3625 (2125–5850)	2000 (601.3–2575)	–
Laser power (mW, median (IQR))	200 (200–312.5)	245 (200–337.5)	–

CRVO (41.2%) and 20 cases were diagnosed with BRVO (58.8%). The median (IQR) value of the total laser spots applied to the retina was 2500 (950–3425) spots and the median value of laser power was 220 (200–312.5) mW. The total number of laser spots was significantly higher in eyes with CRVO compared to the eyes with BRVO (median (IQR), 3625 (2125–5850) spots vs 2000 (601.3–2575) spots, p = 0.005), while there was no significant difference in laser power between two groups (median (IQR), 200 (200–312.5) vs 245 (200–337.5) mW, p = 0.691).

Eyes with RVO that received laser photocoagulation had significantly lower pupil contraction amplitude (mean (SD), 1.14 (0.45) vs 1.27 (0.34) mm, p = 0.037), prolonged contraction latency (median (IQR), 296.5 (256.8–330.5) vs 276.5 (236.3–305.0) ms, p = 0.027), slower contraction velocity (mean (SD), 3.98 (1.47) vs 4.38 (1.29) mm/s, p = 0.043), and slower dilation velocity (median (IQR), 1.56 (1.27–1.91) vs 1.97 (1.62–2.37) mm/s, $p < 0.001$) compared to healthy eyes. There was no significant difference between the two eyes regarding other parameters (Table 2).

In subgroup analysis, eyes with CRVO had lower contraction amplitude (mean (SD), 0.98 (0.52) vs 1.22 (0.40) mm, p = 0.013), and slower dilation velocity (median (IQR), 1.44 (1.25–1.73) vs 2.02 (1.40–2.46) mm/s, p = 0.048) compared to fellow eyes, while eyes with BRVO had slower dilation velocity (median (IQR), 1.65 (1.27–2.02) vs 1.95 (1.78–2.33) mm/s, p = 0.003) compared to fellow eyes. There was no significant difference between the eyes regarding other parameters (Tables 3 and 4).

Correlation analysis revealed that there was a significant inverse correlation between the number of laser spots and pupil dilation velocity (rho = −0.703; p = 0.005) in eyes with CRVO, while no significant correlation was observed in eyes with BRVO.

Among the 14 patients with RVO without laser treatment, who were evaluated for control purposes, nine patients were diagnosed with CRVO (64.3%) and five patients were diagnosed with BRVO (35.7%). No significant difference was observed between laser-treated group and laser-untreated group in terms of the type of RVO (p = 0.207). There were no significant differences in any of the pupillary light reflex parameters between both eyes in non-laser-treated RVO cases (Table 5).

Discussion

Retinal laser photocoagulation aims to resolve tissue hypoxia by disrupting the external layers of the retina containing the photoreceptor layer and increase oxygen passage from the choroid to the inner layers.[11–13] Short ciliary nerves which play a role in the efferent pathway of the pupillary light reflex originate from ciliary ganglia, and advance through the suprachoroidal space to reach the iris and ciliary body. It has been suggested that ciliary nerves may undergo thermal damage in the suprachoroidal region during laser photocoagulation therapy.[14–16] Parasympathetic denervation, which occurs when ciliary nerves are affected, leads to impaired light reflex, tonic pupils, and accommodation loss. Patel et al.[7] presented four cases in which the

Table 2. Pupillary light reflex responses in laser-treated eyes and fellow eyes of patients with retinal vein occlusion.

	Laser-treated eye (*n* = 34)	Fellow eye (*n* = 34)	*p* value
Initial pupil diameter (mm)	4,79 ± 0.75	4.87 ± 0.69	0.389[a]
Contraction amplitude (mm)	1.14 ± 0.45	1.27 ± 0.34	0.037[a]
Contraction latency (ms)	296.5 (256.8–330.5)	276.5 (236.3–305.0)	0.027[b]
Contraction duration (ms)	590.0 (540.3–643.8)	627.0 (542.0–728.8)	0.081[b]
Contraction velocity (mm/s)	3.98 ± 1.47	4.38 ± 1.29	0.043[a]
Dilation latency (ms)	869.0 (825.8–966.0)	899.5 (821.8–963.5)	0.857[b]
Dilation duration (ms)	1554.5 (1458.8–1659.8)	1540.0 (1467.8–1635.3)	0.578[b]
Dilation velocity (mm/s)	1.56 (1.27–1.91)	1.97 (1.62–2.37)	<0.001[b]

Data are expressed as mean ± standard deviation for parametric data and median (1st–3rd quartiles) for non-parametric data.
[a]Paired samples *t*-test.
[b]Wilcoxon signed rank test.

Table 3. Pupillary light reflex responses in laser-treated eyes and fellow eyes of the subset of patients with central retinal vein occlusion.

	Laser-treated eye (*n* = 14)	Fellow eye (*n* = 14)	*p* value
Initial pupil diameter (mm)	4.68 ± 0.54	4.67 ± 0.68	0.928[a]
Contraction amplitude (mm)	0.98 ± 0.52	1.22 ± 0.40	0.013[a]
Contraction latency (ms)	318.5 (232.8–335.5)	289.0 (252.0–341.0)	0.209[b]
Contraction duration (ms)	590.0 (535.5–670.3)	628.0 (552.0–729.0)	0.470[b]
Contraction velocity (mm/s)	3.56 ± 1.65	4.07 ± 1.24	0.111[a]
Dilation latency (ms)	901.5 (829.5–945.0)	902.5 (831.8–963.5)	0.802[b]
Dilation duration (ms)	1534.5 (1227.8–1638.0)	1533.0 (1467.8–1612.8)	0.198[b]
Dilation velocity (mm/s)	1.44 (1.25–1.73)	2.02 (1.40–2.46)	0.048[b]

Data are expressed as mean ± standard deviation for parametric data and median (1st–3rd quartiles) for non-parametric data.
[a]Paired samples *t*-test.
[b]Wilcoxon signed rank test.

Table 4. Pupillary light reflex responses in laser-treated eyes and fellow eyes of the subset of patients with branch retinal vein occlusion.

	Laser-treated eye (*n* = 20)	Fellow eye (*n* = 20)	*p* value
Initial pupil diameter (mm)	4.87 ± 0.87	5.01 ± 0.67	0.190[a]
Contraction amplitude (mm)	1.25 ± 0.36	1.30 ± 0.31	0.534[a]
Contraction latency (ms)	281.0 (264.3–325.8)	274.5 (214.3–302.0)	0.067[b]
Contraction duration (ms)	590.0 (539.5–640.5)	615.5 (542.0–720.5)	0.079[b]
Contraction velocity (mm/s)	4.28 ± 1.29	4.60 ± 1.30	0.214[a]
Dilation latency (ms)	865.0 (811.3–968.3)	897.0 (801.5–962.8)	0.881[b]
Dilation duration (ms)	1589.0 (1496.8–1661.3)	1565.5 (1469.8–1640.5)	0.765[b]
Dilation velocity (mm/s)	1.65 (1.27–2.02)	1.95 (1.78–2.33)	0.003[b]

Data are expressed as mean ± standard deviation for parametric data and median (1st–3rd quartiles) for non-parametric data.
[a]Paired samples *t*-test.
[b]Wilcoxon signed rank test.

pupil remained dilated for 6–18 months following panretinal laser treatment performed under subtenon anesthesia. They concluded that the anesthesia may have lead to unintended burn in the choroidal nerves without notice to the patient, while the topical anesthesia may have a protective effect by the warning effect of the pain felt by the patient. Our patients had been treated under topical anesthesia and the power of the laser was not increased more than the pain threshold. Lobes and Bourgon[17] reported 22 cases with pupillary abnormalities following laser treatment, in which all patients showed sectoral palsy of the iris sphincter, 15 patients had hypersensitivity towards 0.125% pilocarpine, four patients had accommodation paralysis, and six patients had light-near dissociation. Ebrahim et al.[18] reported a case of tonic pupil which developed after pars plana vitrectomy and endolaser procedure.

Table 5. Pupillary light reflex responses in patients with retinal vein occlusion (RVO) without laser treatment.

	Eyes with RVO without laser treatment (n = 14)	Fellow eye (n = 14)	p value
Initial pupil diameter (mm)	4.97 ± 0.67	4.72 ± 0.67	0.209[a]
Contraction amplitude (mm)	1.35 ± 0.44	1.46 ± 0.30	0.263[a]
Contraction latency (ms)	252.0 (224.0–308.8)	279.0 (218.5–303.5)	0.778[b]
Contraction duration (ms)	616.5 (525.3–722.3)	589.5 (531.8–633.8)	0.331[b]
Contraction velocity (mm/s)	4.95 ± 1.47	5.09 ± 1.0	0.651[a]
Dilation latency (ms)	864.0 (792.0–978.3)	866.0 (800.0–901.0)	0.330[b]
Dilation duration (ms)	1507.0 (1379.0–1612.8)	1627.0 (1487.0–1646.3)	0.116[b]
Dilation velocity (mm/s)	2.49 (1.73–3.05)	2.24 (1.81–3.35)	0.683[b]

Data are expressed as mean ± standard deviation for parametric data and median (1st–3rd quartiles) for non-parametric data.
[a]Paired samples t-test.
[b]Wilcoxon signed rank test.

Kaufman[4] performed retinal photocoagulation on the horizontal meridian in monkeys and found that parasympathetic fibers were initially carried by several short ciliary nerves. He reported that the severity of the morphological changes in the nerves passing through the choroid depended directly on the intensity of the laser burn and the proximity of the nerve to the burn. One study that conducted a histopathological comparison of diode and argon laser lesions in rabbit retina reported that diode laser lesions in choroid and retinal layers were closer to ciliary nerves and more traumatic.[19]

Yilmaz et al.[20] examined pupillary responses with automated infrared pupillometry in diabetic retinopathy cases who underwent panretinal photocoagulation. Subjects were divided into two groups, as those who underwent conventional laser treatment and those who underwent PASCAL laser treatment. Both groups showed significant increase in basal measurements of pupil diameters in all lighting conditions, and that the conventional laser treatment group was affected more than the PASCAL laser group. They concluded that conventional laser treatment caused more intense laser burns compared to the PASCAL laser and caused more damage to the ciliary nerves. In another study by Yilmaz et al.,[21] in which patients with diabetic retinopathy who underwent panretinal photocoagulation and focal laser photocoagulation were assessed with automated infrared pupillometry; it was reported that the panretinal photocoagulation group had significantly increased basal measurements of pupil diameters in all lighting conditions, while there was no significant change in the focal laser photocoagulation group. Although there are studies in the literature which examine the effects of laser photocoagulation on pupil diameter, there is lack of evidence on dynamic pupil responses in eyes with retinal vein occlusion that underwent retinal laser photocoagulation. It is also known that ischemia, death of ganglion cells, and axonal degeneration occurring in retinal vein occlusion cause loss of retinal nerve fibers.[22,23] Therefore, the afferent pathway of the pupillary light reflex is also expected to be affected in RVO patients. In this study, we observed that there was no significant difference between the two eyes of RVO patients that did not receive laser treatment, who were included in the study for control purposes.

Limitations of this study are the relatively small sample size in each RVO group and the cross-sectional nature of the study design which precludes us to draw firm conclusions about whether the changes in pupillary responses are solely the consequences of laser treatment or there is a contributing effect of retinal ischemia itself, although we did not observe similar changes in non-laser-treated control cases. This study concludes that the eyes with RVO that received retinal laser photocoagulation had lower pupil contraction amplitude, prolonged contraction latency, and slower contraction and dilation velocities. Longitudinal studies on retinal vein occlusion will allow the possibility of revealing the changes in pupillary light reflex responses by evaluating the measurements taken before and after laser treatment.

Authors' note

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Declaration of conflicting interests

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