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A cross-sectional evaluation of static pupil diameter under different illumination conditions in branch retinal vein occlusion

Retinal ven dal tıkanıklığında farklı ışık koşullarında pupil çapının kesitsel değerlendirilmesi

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ABSTRACT

Aim: To evaluate the effect of branch retinal vein occlusion (BRVO) on pupil diameter under varying lighting conditions.

Materials and Methods: This cross-sectional study included patients diagnosed with BRVO. All participants underwent comprehensive ophthalmologic examinations, including optical coherence tomography and fluorescein angiography. Pupil diameters were measured under scotopic, mesopic, photopic, and pharmacologic mydriatic conditions using the Sirius device (CSO; Sirius, Italy). Eyes affected by BRVO were compared with the contralateral unaffected eyes.

Results: Sixty eyes from 30 patients (mean age: 59.06±12.09 years) were included. Among the affected eyes, 17 (56.67%)13(43.33%) had occlusion at the superior temporal vein and 13 (43.33%) at the inferior temporal vein. Pupil diameters under different lighting conditions showed no statistically significant differences between BRVO affected and contralateral eyes. The mean pupil diameter under scotopic conditions was 4.87±0.98 mm in BRVO eyes and 4.47±0.98 mm in fellow eyes. Under mesopic conditions, it was 3.76±0.90 mm in BRVO eyes and 4.08±0.88 mm in fellow eyes. Photopic measurements showed 3.27±0.72 mm in BRVO eyes and 3.06±0.40 mm in fellow eyes. Finally, under pharmacologically induced mydriasis, pupil sizes were 7.87±0.70 mm in BRVO eyes and 7.76±0.68 mm in fellow eyes. These findings indicate that BRVO does not significantly alter pupil size in response to varying illumination or pharmacological dilation.

Conclusions: The impairment and the changes of pupillary reflex known to be a prognostic criterion for retinal vein occlusion, however this seem to be preserved in BRVO. Based on the results of this study BRVO was not associated with significant alterations in static pupil diameter under different lighting or pharmacologic dilation conditions.

Keywords: Branch retinal vein occlusion, pupil size, pupil diameter

ÖZ

Amaç: *Bu çalışmanın amacı, retinal ven dal tıkanıklığının (RVDT) farklı aydınlatma koşullarında pupilla boyutu üzerine etkisini araştırmaktır.*

Gereç ve Yöntem: *Kesitsel planlanan bu çalışmaya RVDT tanısı alan hastalar dahil edildi. Optik koherens tomografi ve fundus flöresein anjiografisi dahil olmak üzere ayrıntılı oftalmolojik muayene gerçekleştirildi. Skotopik, mezopik, fotopik ve farmakolojik midriyazis koşullarında pupilla çapları Sirius cihazı (CSO; Sirius, Floransa, İtalya) kullanılarak ölçüldü. RVDT tanılı gözler, etkilenmemiş karşı gözlerle karşılaştırıldı.*

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Bulgular: *Toplam 30 hastaya ait 60 göz çalışmaya dahil edildi. Hastaların ortalama yaşı 59,06±12,09 yıl idi. Tıkanıklık yeri 17 gözde (%56,67) üst temporal ven, 13 gözde (%43,33) ise alt temporal ven olarak saptandı. Skotopik (4,87±0,98 mm, 4,47±0,98 mm), mezopik (3,76±0,90 mm, 4,08±0,88 mm), fotopik (3,27±0,72 mm, 3,06±0,40 mm) ve midriyatik (7,87±0,70 mm, 7,76±0,68 mm) koşullarda ölçülen pupilla çapları, sağlıklı gözlerle karşılaştırıldığında, istatistiksel olarak anlamlı bir fark saptanamadı.*

Sonuç: *Pupilla refleksindeki farklılıklar ve değişiklikler, retinal ven tıkanıklığında prognostik bir kriter olarak bilinmektedir; ancak bu bulgular ven dal tıkanıklığında korunmuş olarak görünmektedir. Bu çalışmanın sonuçlarına göre, retinal ven dal tıkanıklığının farklı aydınlatma koşullarında pupilla çapını etkilemediği gösterilmiştir.*

Anahtar Sözcükler: *Retinal ven dal tıkanıklığı, pupilla boyutu, pupilla refleksi*

INTRODUCTION

Branch retinal vein occlusion (BRVO) is the second most common retinal vascular disorder after diabetic retinopathy and represents a significant cause of visual impairment worldwide (1). It is frequently associated with systemic comorbidities such as hypertension, diabetes mellitus, and atherosclerosis. Clinically, BRVO typically presents with painless vision loss and characteristic retinal haemorrhages and exudates detected on dilated fundus examination. Unlike central retinal vein occlusion (CRVO), which often results in extensive retinal ischaemia and widespread functional impairment, BRVO generally causes sectoral retinal involvement due to localized venous obstruction (2).

The pupillary light reflex depends on the integrity of the afferent retinal pathway, particularly the retinal ganglion cells that transmit signals through the optic nerve to the pretectal nuclei (3). In retinal vein occlusion, ischaemic damage may impair this pathway, especially in cases with extensive retinal nonperfusion (1). In CRVO, relative afferent pupillary defect (RAPD) is a well-recognized clinical finding and has been associated with the degree of retinal ischaemia and visual prognosis. Similarly, alterations in pupillary parameters have been reported in other retinal diseases such as diabetic retinopathy and age-related macular degeneration (4,5). However, in BRVO, where ischaemia is typically confined to a limited retinal sector, it remains unclear whether this localized damage is sufficient to affect pupillary function.

Understanding pupillary behaviour in BRVO may provide additional insight into the functional impact of sectoral retinal ischaemia and may have clinical relevance in assessing retinal integrity. Despite this potential importance, data evaluating pupillary parameters specifically in BRVO are scarce.

Therefore, the aim of this study was to evaluate whether BRVO is associated with alterations in static pupil diameter under different illumination conditions compared with contralateral healthy eyes.

MATERIALS and METHODS

This prospective cross-sectional study was conducted after approval of Committee of Ethics (Kafkas University, Committee of Ethics, 2014/11/122) and in accordance with the Helsinki Declaration. Consecutive patients who referred from the emergency department due to sudden visual loss to ophthalmology department and diagnosed with BRVO, between January 2015 and September 2015 were enrolled in the study. After the initial evaluation, eligible patients were informed about the study. Those who agreed to participate were asked to sign a written informed consent form.

Patients underwent a detailed ophthalmological examination including best-corrected visual acuity (BCVA) measurement recorded in logMAR units, intraocular pressure measurement using Goldmann applanation tonometry, and anterior and posterior segment evaluation after pupillary dilation.

Patients with a history of intravitreal injection or laser therapy, diagnosed with anisometropia, previous diagnosis of glaucoma, retinal disease or uveitis, asymmetrical cataract presentation, any previous ocular trauma or surgery, any routine eye-drop usage were excluded from the study. Also, patients with any kind of disorder may cause neuropathy such as Guillain-Barre Syndrome, multiple sclerosis or diabetes mellitus were excluded from the study.

Imaging

Optical coherence tomography (Optovue OCT, Fremont, CA) and fluorescein angiography (Canon FFA, Japan) imaging were performed. After the approval of the diagnosis of BRVO, pupillary diameter measurement with Sirius device (CSO, Florence, Italy) in scotopic (0.4 lux), mesopic (4 lux), and photopic (50 lux) conditions were performed. The last measurement of the pupil was performed 45 minutes after pupil dilatation with tropicamide (Tropamid, 0.05%, Bilim, Turkey) and phenylephrine hydrochloride (Mydfrin, 2.5%, Alcon, Switzerland). To minimize the potential effect of diurnal variation on pupil size, measurements were obtained during the same time interval of the day and in the same examination room for all participants. Patients were allowed to adapt to the ambient lighting conditions before each measurement. Sirius device is able to complete the measurements automatically in scotopic (0.4 lux), mesopic (4 lux) and photopic (40 lux) conditions. Previous validation studies have demonstrated that pupil diameter measurements obtained with the Sirius anterior segment analyser exhibit high intra-device repeatability under standardized lighting conditions, supporting the reliability of pupillary measurements performed with the same instrument (6).

Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL). The distribution of the variables was assessed using the Kolmogorov–Smirnov test. Since the data showed normal distribution, parametric tests were applied. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as percentages.

Comparisons between BRVO-affected eyes and fellow eyes of the same patients were performed using the paired samples t-test. Comparisons between superior and inferior BRVO groups, which involved different patients, were performed using the independent samples t-test. A p-value <0.05 was considered statistically significant.

In addition, a sensitivity power analysis was performed to determine the detectable effect size with the available sample.

RESULTS

For this prospective cross-sectional study, 60 eyes of 30 patients were evaluated at the time of initial BRVO diagnosis. Male-to-female ratio was 1:1 with a mean age of 59.06±12.09 (35-83) years. The main comorbidity was systemic hypertension (n=14). The distribution of comorbidities is presented in (Table-1).

BRVO was diagnosed in the right eye in 17 patients (56.7%) and in the left eye in 13 patients (43.3%). For 17 eyes (56.7%) the affected area was superior macula while for 13 inferior macula. Based on fluorescein angiography findings, none of the included eyes demonstrated extensive retinal nonperfusion exceeding 5 disc diameters, and no case required laser treatment for ischemia. The mean best corrected visual acuities for healthy eyes and affected eyes were 0.11±0.24 (1.0-0.0) logMAR and 0.33±0.44 (1.3-0.0) logMAR. In healthy eyes of patients, cataract was the only diagnosis which may cause visual impairment, and it did not differ clinically from the affected eye in each individual. Twenty-eight affected eyes (93%) were diagnosed with macular oedema based on OCT and clinical examination.

Pupil diameters measured under different lighting conditions in BRVO and fellow eyes are presented in Table-2. No statistically significant differences were detected between BRVO-affected and contralateral eyes under photopic (p=0.179), mesopic (p=0.161), scotopic (p=0.130), or pharmacologic mydriasis conditions (p=0.549).

Besides, eyes were also compared according to the localization of the occlusion. No statistically significant difference was observed between superior and inferior affected eyes in any of lighting conditions. Mean values and corresponding p-values are presented in Table-3.

Sensitivity analysis indicated that the current sample size provided 80% power to detect moderate effect sizes (Cohen's dz ≈ 0.56).

Table-1. Distribution of the comorbid diseases

Systemic Disease	Number of Patients	Percentage (%)
Systemic Arterial Hypertension	14	46.67
Hyperlipidaemia	3	10.00
Hypercholesterolemia	1	3.33
Coronary Artery Disease	3	10.00

Table-2. Measured pupil sizes in different conditions. Values with standard deviation and minimum maximum.

Pupil size	Study Eyes	Control eyes	p Value
Photopic	3.27±0,72 mm (4.96-2.03)	3.06±0,40 mm (4.49-1.75)	0.179
Mesopic	4.08±0,88 mm (5.89-2.41)	3.76±0,90 mm (5.73-2.29)	0.161
Scotopic	4.87±0,98 mm (6.89 – 3.09)	4.47±0,98 mm (6.87-2.55)	0.13
Pharmacologic mydriasis	7.76±0,68 mm (8.99 – 5.90)	7.87±0,72 mm (9.20-6.10)	0.549

Table-3. Comparison of pupil sizes according to the occlusion site

BRVO Location	Photopic	Mesopic	Scotopic	Mydriatic
Superior Temporal Quadrant	2.81±0.42	3.66±0.84	4.42±0.91	7.87±0.62
Inferior Temporal Quadrant	2.92±0.41	3.87±1.01	4.51±1.18	7.87±0.87
p-value	0.451	0.554	0.81	0.988

DISCUSSION

Branch retinal vein occlusion is related to severe complications which may cause visual impairment (7). While CRVO itself is well-studied in the current literature, particularly regarding its effects on the pupillary response and the commonly known ischaemic result as relative afferent pupillary defect, there is insufficient data on BRVO (8). Based on the results of this study the effect of BRVO on pupillary diameter is examined and no significant relationship was observed.

BRVO is known to present in elderly patients with an almost equal female to male ratio. However, for younger patients aged less than 50 years, there is a female dominance (9). When compared to the literature data, the mean age of patients in current study seems to be lower. The region where the study was conducted is located approximately 1700 meters above sea level which may cause slightly elevated haematocrit values and polycythaemia. The moderately lower mean age observed in this cohort may be influenced by such environmental or demographic factors, including the higher altitude of the region where the study was conducted. Although data regarding the association between high altitude and earlier onset of CRVO or BRVO are limited, several reports have described relatively younger patients presenting with retinal vein occlusion, some in their mid-30s (10,11). Hansen et al. (12) also reported an earlier onset of retinal vein occlusion in populations living at higher altitudes. Nevertheless, further studies are required to clarify this potential relationship. The female-to-male ratio in our study was consistent with the existing literature.

The main comorbidity for BRVO is revealed as systemic hypertension in the current literature. Diabetes and atherosclerosis are other commonly associated conditions (13). Moreover, thrombotic factors like hyperlipidaemia, hypercholesterolemia, thrombophilia, and use of oral contraceptive drugs are associated with retinal thrombosis (14). This study has parallel results with the mentioned data according to accompanied diseases, major detected one was hypertension followed by hyperlipidaemia, coronary heart disease and hypercholesterolemia. These systemic conditions may contribute to the development of BRVO through endothelial dysfunction, increased vascular rigidity, and structural alterations at arteriovenous crossing sites. In particular, systemic hypertension may promote arteriolar wall thickening and compression of the adjacent vein, leading to turbulent flow, venous stasis, and thrombus formation (14).

The localization of the BRVO is commonly expected to be in the superior temporal quadrant due to higher frequency of arteriovenous crossings (15). Hayreh et al. (16) declared a 61.8% ratio for superior temporal occlusion. In line with the literature, in the current study 56.7%

(n=17) of the eyes were affected in the superior temporal quadrant.

In BRVO, the main causes of visual impairment are macular oedema, macular hypoperfusion and complications due to neovascularization (7). Macular oedema may contribute to photoreceptor dysfunction and disruption of outer retinal integrity, potentially influencing afferent retinal signalling (17). Therefore, in theory, oedema-related structural changes could be expected to affect pupillary parameters. However, despite the high prevalence of macular oedema in this cohort, no significant alterations in pupil diameter were observed. This finding may suggest that, in BRVO, localized macular involvement alone may not be sufficient to cause clinically measurable impairment in pupillary size responses. Nevertheless, future studies including distinct subgroups of oedematous and non-oedematous BRVO cases would help clarify whether the presence and severity of macular oedema have a measurable impact on pupillary parameters.

Pupillary function reflects the integrity of the afferent retinal pathway, particularly the retinal ganglion cells that transmit signals through the optic nerve. In several retinal vascular and degenerative diseases, impaired pupillary responses have been associated with increased ischemic burden and worse visual prognosis (18). In contrast, in CRVO especially in ischemic cases, pupillary dysfunction is a well-established clinical marker with important prognostic implications, whereas comparable evidence in BRVO is scarce.

In BRVO, pathophysiological changes arise from localized ischemia affecting a limited retinal sector. Although macular oedema and localized dysfunction of photoreceptors and ganglion cells may occur, substantial retinal areas typically remain functionally preserved. Since the pupillary light reflex represents a summative response of global retinal input, sectoral ischemia may not be sufficient to produce measurable alterations in pupil diameter when widespread nonperfusion is absent (19). In cases where haemorrhages or ischaemic perfusion are localized, notably in BRVO, there may be a preservation of pupillary responses due to intact sections of the retinal ganglion cell layer that contribute to the reflex pathway. In this cohort, no extensive ischemia was observed, which may explain the preservation of pupillary parameters despite localized retinal involvement.

Clinically, the size and responsiveness of the pupil in BRVO patients did not exhibit significant statistical differences from fellow eyes, but the preservation of pupillary response has considerable clinical relevance. Such findings can be crucial indicators of maintained retinal functionality despite underlying structural damage (20). The pupillary response serves as a valuable marker, providing insights into the functional state of the retina and the potential for recovery or response to therapeutic interventions.

Moreover, maintaining an appropriate pupillary size and reactivity suggests that a threshold of retinal ischaemia has not been crossed, which could lead to more severe visual impairments and complications such as neovascularization, characterized by deteriorating blood supply and resultant retinal disturbances (21,22). However, the prognostic significance of static pupil diameter measurements in BRVO remains unclear. Further longitudinal studies are needed to determine whether pupillary parameters have predictive value for visual outcomes or treatment response.

CONCLUSION

In CRVO, pupillary reflex and light response could be damaged. Afferent pupillary defect is a well-known entity related to ischaemia level after the occlusion and it is a result of retinal dysfunction in cellular scale (23). While this impairment in CRVO is studied in current literature, the data related to BRVO in this subject is insufficient. This study hypothesizes that afferent damage related to insufficient perfusion of photoreceptors, bipolar neurons and ganglion cells may result in pupil response abnormalities. In this cohort, BRVO was not associated with measurable alterations in static pupil diameter. The segmental nature of branch occlusion results in a relatively limited degree of ischaemia, which may be insufficient to disrupt pupil diameter regulation. To the best of our knowledge, this study represents one of the few studies evaluating the effect of BRVO on pupil size. However, no direct functional or ischemic assessment of the pupillary pathway was performed in the present study. The absence of dynamic pupillary measurements and detailed ischemic classification should be considered important limitations when interpreting the relationship between BRVO and pupillary function.

The main limitations of the study include the limited number of patients and the lack of longitudinal follow-up data. Given the sample size,

the study may have been underpowered to detect small effect sizes, and later follow-up assessments might reveal significant differences. Additionally, the use of the fellow eye as a control may be influenced by systemic vascular factors or bilateral subclinical retinal involvement, which could potentially affect both eyes. Although patients with diabetes mellitus were excluded due to its known effects on pupillary response and autonomic function, this exclusion criterion may limit the generalizability of the findings. Furthermore, because extensive retinal ischemia was not observed in this cohort, the results may not be applicable to patients with ischemic BRVO. Finally, the wide age range of participants may have influenced the results, and this limitation could be addressed in future studies with larger and more homogeneous populations.

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Consent to Participate: Informed consent was obtained from all individual participants included in the study

Ethics Approval: This study was conducted after the approval of the Ethics Committee of Kafkas University (2014/11/122) and in line with the principles of the Declaration of Helsinki

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