• Clinical Research •

Disorganization of the retinal inner layers as a prognostic factor in eyes with central retinal artery occlusion

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Abstract

• AIM: To evaluate baseline foveal disorganisation of retinal inner layers (DRIL) as a prognostic factor in eyes with central retinal artery occlusion (CRAO).

• METHODS: Twenty-eight CRAO patients who were followed-up between 2010 and 2016 were retrospectively investigated. Demographic characteristics and detailed ophthalmological examination findings of all patients were recorded. Macular thicknesses (MTs) from 5 separate spots and DRIL were measured with spectral-domain optic coherence tomography (SD-OCT). Correlations between DRIL score and logMAR converted visual acuity (VA), change in VA, patient reference time (RT), number of hyperbaric oxygen therapy (HBOT) sessions, MT and MT change were investigated.

• RESULTS: There was a positive correlation between the DRIL score and the final VA (*r*=0.787) and a negative correlation with the change in VA (*r*=-0.763). The RT and MT were closely related to the DRIL score. A negative correlation was found between the number of HBOT sessions and the DRIL score (*r*=-0.341).

• CONCLUSION: The DRIL score is a parameter assessed by SD-OCT, which can provide us reliable information regarding the prognosis of visual functions and response to the treatment for CRAO patients at acute phase.

• KEYWORDS: central retinal artery occlusion; disorganisation; inner retina; spectral-domain optic coherence tomography; prognosis

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INTRODUCTION

Central retinal artery occlusion (CRAO) is a rare disease of the eye that could cause catastrophic result. Up-to-date treatment algorithms are not enough for this disease and there are still ongoing studies for new treatments. Moreover, there is not enough data to understand the prognosis. Hayreh and Zimmerman[1] described that the most important factor is the type of the disease, but no reliable methods exist to determine which individuals with CRAO will gain or lose vision over time and which individuals could respond well to the treatments.

The noninvasive, easily performed imaging method of spectral-domain optical coherence tomography (SD-OCT) ensures reliable, high-quality and high-resolution imaging of retinal structures. Previous studies showed that at acute phase, macular thickness (MT) is not correlated with the final visual acuity (VA) of CRAO but it is correlated with the final MT and macular thickness change (MTC)[2]. It is very important to find out new reliable parameters to understand the prognosis of CRAO at the acute phase of the disease and its respond to treatment modalities.

Studies in diabetic macular edema (DME) revealed that disorganisation of retinal inner layers (DRIL) is an important factor for visual prognosis[3-4]. DRIL was also found to be sensitive and specific diagnostic parameter of capillary non-perfusion in diabetic retinopathy[5]. It is very likely to find out the same results with CRAO patients. In this study, we evaluated baseline foveal DRIL and other SD-OCT parameters to assess how they predict VA in eyes with CRAO.

SUBJECTS AND METHODS

Ethical Approval The study protocol was approved by the Kecioren Training and Research Hospital Ethical Committee and adhered to the tenets of the Declaration of Helsinki. This was a single-site, retrospective cohort study made in Ophthalmology Department of the Gulhane Military Medical School, which is a tertiary center with a hyperbaric oxygen therapy (HBOT) unit. Written informed consent was taken from all the subjects after explaining the nature of the study.

Study Subjects The medical charts of patients who followed up between January 2010 and January 2016, in Ophthalmology Department of Gulhane Military Medical School, were retrospectively reviewed. Inclusion criteria were: 1) diagnosis

of acute CRAO; 2) completed follow up more than 3mo; 3) having fluorescein angiography (FFA), SD-OCT and fundus photography at the initial visits. Exclusion criteria were: 1) anterior segment diseases such as cataract and corneal opacities that reduces the quality of the FFA and SD-OCT images; 2) posterior segment diseases such as macular degeneration and vitreomacular traction; 3) optic coherence tomography (OCT) image quality score <7; 4) cilioretinal artery sparing.

All subjects underwent standard threatment including ocular massage (repeated manual compression for 10s followed by sudden release, for 10min), anti-glaucomatous agents (topical timolol and dorzolamide combination drops and intravenous 20% mannitol 100 mL), anti-platelet aggregating agents (oral acetylsalicylic acid 100 mg). All subjects were also referred immediately to the Undersea and Hyperbaric Oxygen unit and underwent HBOT sessions. The HBOT sessions were terminated when there is no change in VA for last 2 sessions.

Demographic Data and Ophthalmic Examinations All subjects' demographic data were recorded. All patients in this study had detailed ophthalmic exeminations including best corrected visual aquity (BCVA) by logMAR chart, slit-lamp biomicroscopy, non-contact tonometry, fundus photography, FA and SD-OCT. OCT examinations were perfomed by Spectralis (Hidelberg Engineering, Germany) and FAs were performed by HRA (Hidelberg Engineering, Germany) at each visit by the same technician.

The difference between the first and last BCVA was recorded. The increase of 0.3 or more was accepted as clinically significant increase of the BCVA[6].

Macular Thickness Measurement The MT was calculated manually at the foveal scan at 5 seperate points because most patients could not fixate the fovea due to severely impaired VA. Five seperate points were foveal thickness (FT), nasal parafoveal thickness (NpaT; 500 μm away nasally from the fovea), nasal perifoveal thickness (NpeT; 1500 μm away nasally from the fovea), temporal parafoveal thickness (TpaT; 500 μm away temporally from the fovea) and temporal perifoveal thickness (TpeT; 1500 μm away temporally from the fovea). MTs in both eyes measured at initial and final OCT examinations. MTC (first MT－last MT) was calculated by using SPSS ver. 21 (IBM, Armonk, New York, USA).

Definition and Analysis of the Disorganisation of Retinal Inner Layers The SD-OCT scan passing through the foveal center was selected along with 3 B-scans immediately above and below, for a total of 7 scans. DRIL was defined as the inability to identify any boundaries between the ganglion cell-inner plexiform layer complex, inner nuclear layer, and outer plexiform layer. This definition of the DRIL is maintained from Nicholson *et al*[5]. For each 7 scans DRIL was searched in 1000 μm centered the fovea and for each scan if the detected DRIL was grater than 500 μm, that scan accepted as DRIL (+) (Figure 1) than the score of DRIL calculated by accumulating the DRIL (+) scans. All subjects have been scored between 0 [no DRIL (+) scan] to 7 [all scans are DRIL (+)].

After all the OCT examinations recorded, correlations between the possible prognostic factors such as age, reference time (RT) to the clinic, mean MT, MTC, DRIL scores and VA measurements were analysed. The correlations between the number of HBOT sessions, VA measurements and DRIL scores were also analyzed.

Statistics SPSS ver. 21.0 (IBM, Armonk, New York, USA) was used to analyze data. Standard deviations, means, percents were made to identificate the data. The *t*-test or Mann-Whitney *U* test was used to compare the before and after data. Correlations between the data were maintained by Pearson's correlation test. $P<0.05$ considered statistically significant in this study.

Table 1 Patient baseline characteristics

Parameters	Data
Age (y), mean±SD	63.39±13.86
Gender, *n* (%)	
F	12 (42.8)
M	16 (57.2)
Bilaterality, *n* (%)	
R	15 (53.6)
L	13 (46.4)
Referance time (h), mean±SD	22.3±7.8
Follow up time (mo), mean (min-max)	11.39 (3-30)
IOP, mean±SD	14±3.32

RESULTS

Twenty-eight eyes of 28 patients were studied. Participants had a mean age of 63.39±13.86y. Mean (min-max) follow-up time was 11.39 (3-30)mo. Forty-two percent of the participants were female and 53.6% of the affected eyes were right side. The mean application time to the clinic after the first symptoms occurred (RT) was 22.3±7.8h. Patients baseline characteristics including intraocular pressure (IOP) are presented in Table 1.

At the first examination mean BCVA was 2.68±0.73 and it was 1.82±1.03 for the last. The increase of the BCVA was statistically different ($P<0.01$). The mean difference between first and last BCVAs was 0.85±0.97. Improvement of the VA was clinically significant for 17 (60.7%) patients.

Macular Thickness The mean MT at the initial and final OCT examinations for both eyes and mean MTC for the affected eyes are presented in Table 2. For the affected eye, the MT at the first examinations were much thicker than MT at the last examinations ($P<0.01$). The affected eyes' MT were thicker then the fellow eyes' MT at the first examination and thinner at the last ($P<0.01$).

Disorganisation of Retinal Inner Layers DRIL scores' distribution is presented in Table 3. Due to imbalance of the

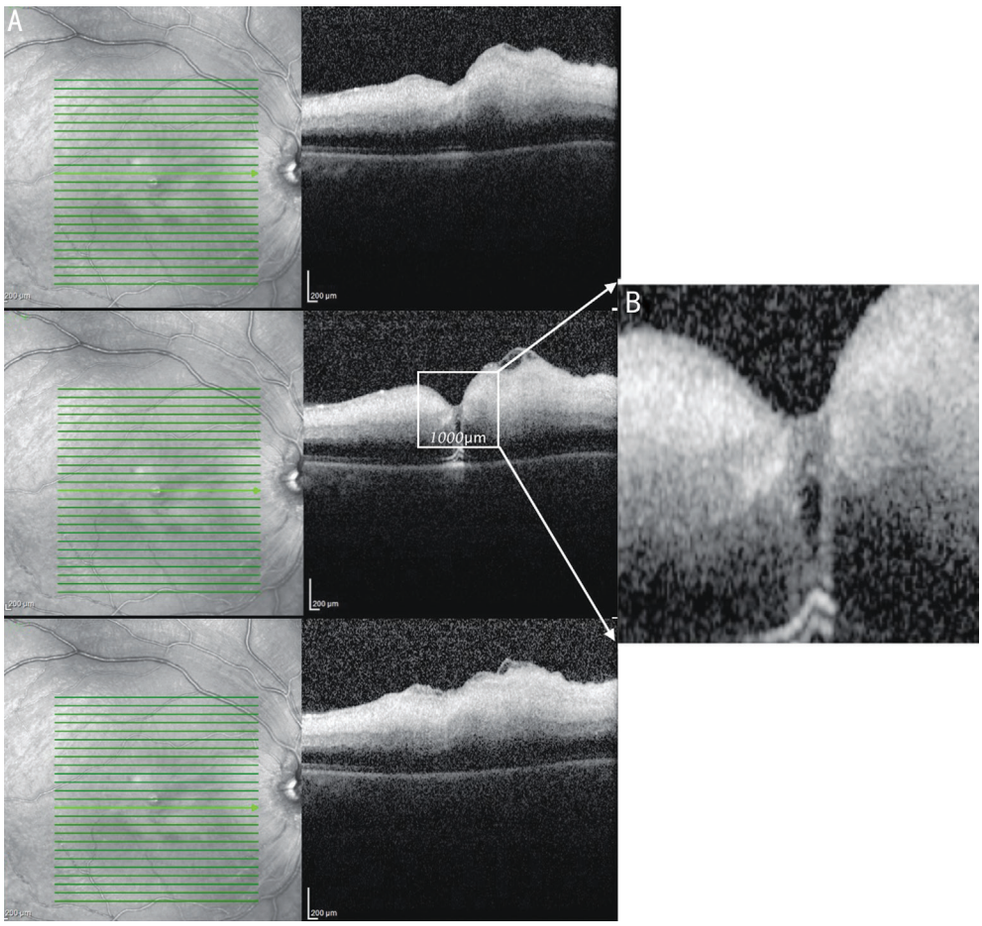

Figure 1 Determining the DRIL of a patient with CRAO A: Central 3 OCT images; B: Magnified central 1000 µm section of the fovea. As shown in this figure the boundaries of retinal inner layers could not be distinguished.

Table 2 The affected and the fellow eyes' mean MT at the initial and final exams and MTC

MT locations	Affected eye	Fellow eye	MTC	P^a	P^b
FT, first	293.1 (159)	196.4 (26.1)	107.8	0.001	<0.01
FT, last	185.3 (60.4)	202.5 (51.1)			0.005
NPaT, first	435.8 (132.5)	273.6 (25.1)	223.1	<0.01	<0.01
NPaT, last	212.7 (43.5)	274.4 (35.2)			<0.01
TPaT, first	399 (121.3)	275.1 (28.6)	192.1	<0.01	<0.01
TPaT, last	206.9 (54.7)	272.5 (41.3)			<0.01
NPeT, first	440 (93.4)	319.9 (28.1)	217.8	<0.01	<0.01
NPeT, last	222.2 (47.8)	309.8 (32.6)			<0.01
TPeT, first	392.3 (98.6)	298.3 (31.7)	189.7	<0.01	<0.01
TPeT, last	202.6 (56)	285 (96)			<0.01

MTC: Macular thickness change, FT: Foveal thickness; NPaT: Nasal parafoveal thickness; TPaT: Temporal parafoveal thickness; NPeT: Nasal perifoveal thickness; TPeT: Temporal perifoveal thickness. [a]Comparison of affected eyes' initial and final mean MT with Wilcoxson Signed Ranks test; [b]Comparison of affected and fellow eyes' mean MT with Wilcoxson Signed Ranks test.

distribution it was impossible to compare scores with each other. Because of this 2 different groups were created. The subjects who had the scores of 0, 1, 2, 3 were included to DRIL-A group, and other scores were included to DRIL-B.

Investigation of the Efficacy of Hyperbaric Oxygen Therapy The correlations between HBOT sessions count, initial and final BCVA were not significant. There was a positive correlation between HBOT sessions and the difference of BCVAs (Pearson's correlation test, r=0.435) and negative correlation with the DRIL score (Pearson's correlation test, r=-0.341).

Investigation of Some Possible Prognostic Factors and DRIL as a Prognostic Factor Correlations between BCVA measurements and possible prognostic factors are presented in Table 4. There were high correlations with all the parameters except initial BCVA, age, the first FT and the first TPeT. The correlations between MTC and BCVA measurements with DRIL score was also analyzed. The correlatios were not significant with the initial BCVA but there were strongly correlated with the final BCVA, difference of BCVAs and DRIL score.

The DRIL score was highly correlated with most of the other prognostic factors except age, the first TPeT and the last FT (Table 5). The comparison of DRIL-A and DRIL-B groups according to the visual function and other prognostic factors is presented in the Table 6. DRIL-A and DRIL-B groups were significantly different from each other for most of the parameters, but there were not significantly difference between

Table 3 Distribition of the score of DRIL

The score of DRIL	0	1	2	3	4	5	6	7
n (%)	0	3 (1)	1 (0.3)	5 (17.8)	1 (0.3)	2 (0.7)	3 (1)	13 (46.4)

DRIL: Disorganization of retinal inner layers.

Table 4 The correlations between the possible prognostic factors and BCVA measurements

Parameters	Initial BCVA	Final BCVA	The difference of BCVAs
Age	-0.078	0.063	-0.126
Referance time	0.124	0.522[b]	-0.464[a]
FT, first	0.005	0.333	-0.351
NPaT, first	0.90	0.395[a]	-0.489[b]
TPaT, first	-0.53	0.375[a]	-0.44[a]
NPeT, first	0.96	-0.525[b]	-0.488[b]
TPeT, first	0.006	0.104	-0.106
FT, last	0.172	-0.387[a]	0.542[b]
NPaT, last	0.047	-0.564[b]	0.637[b]
TPaT, last	0.04	-0.614[b]	0.684[b]
NPeT, last	0.022	-0.67[b]	0.698[b]
TPeT, last	0.56	-0.599[b]	0.68[b]
DRIL score	0.101	0.787[b]	-0.763[b]

BCVA: Best corrected visual acuity; FT: Foveal thickness; NPaT: Nasal parafoveal thickness; TPaT: Temporal parafoveal thickness; NPeT: Nasal perifoveal thickness; TPeT: Temporal perifoveal Thickness; DRIL: Disorganization of retinal inner layers. [a]The correlation is significant at the level of 0.05; [b]The correlation is significant at the level of 0.01.

Table 5 The relations of DRIL score with other prognostic factors

PFs	Age	RT	FT, first	NPaT, first	TPaT, first	NPeT, first	TPeT, first	FT, last	NPaT, last	TPaT, last	NPeT, last	TPeT, last
DRIL Score	0.259	0.482[b]	0.463[a]	0.586[b]	0.549[b]	0.697[b]	0.299	-0.274	-0.630[b]	-0.542[b]	-0.705[b]	-0.555[b]

DRIL: Disorganization of retinal inner layers; PFs: Prognostic factors; RT: Reference time; FT: Foveal thickness; NPaT: Nasal parafoveal thickness; TPaT: Temporal parafoveal thickness; NPeT: Nasal perifoveal thickness; TPeT: Temporal perifoveal Thickness. [a]The correlation is significant at the level of 0.05; [b]The correlation is significant at the level of 0.01.

these 2 groups according to the age, initial BCVA, first TPeT and last FT.

DISCUSSION

CRAO is an analogue of cerebrovascular accident for the eye and it is an ocular emergency. CRAO can cause legal bilindness if it is not treated or the treatment is not enough (Figure 2).

In this study, analyses were performed with the aim of determining prognostic factors in CRAO patients. By this date, there is no doubt that the most important study according to the visual prognosis is Hayreh and Zimmerman[1]'s prospective study in 2005. In that study CRAO was divided into 4 groups: non-arteritic permanent CRAO, non-arteritic transient CRAO, non-arteritic CRAO with cilioretinal artery sparing, and arteritic CRAO. Hayreh and Zimmerman[1] had emphasized that the most important prognostic factor for determining the visual prognosis is the type of the disease. In their study, 82% of the transient CRAO patients had VA improvement while this ratio was 67% for CRAO with cilioretinal artery sparing, 22% for non-arteritic permanent CRAO. In our study we did not categorize our patients like Hayreh did and searched for other prognostic factors independently.

The age, RT, MT (at first and last exam, from 5 seperate

Table 6 The comparison of DRIL-A and DRIL-B groups according to the BCVA measurements and other possible prognostic factors

Parameters	DRIL-A	DRIL-B	*P*[a]
Age	60 (10.7)	65 (15.1)	>0.05
Reference Time	17.4 (4)	24.6 (8.2)	<0.05
Initial BCVA	2.45 (1.02)	2.73 (0.53)	>0.05
Final BCVA	0.65 (0.51)	2.37 (0.68)	<0.01
The difference of BCVA	1.80 (0.87)	0.41 (0.64)	<0.01
FT, first	195.4 (96.6)	339.4 (163.5)	<0.01
NPaT, first	339 (62.7)	481.6 (133)	<0.01
TPaT, first	312.7 (45.3)	439.8 (125.3)	<0.01
NPeT, first	361.8 (41.1)	477.1 (88.6)	<0.01
TPeT, first	360.5 (41.4)	407.4 (114.3)	>0.05
FT, last	215.5 (91.5)	171 (32.2)	>0.05
NPaT, last	249.8 (51.7)	195.2 (25.3)	<0.01
TPaT, last	253.2 (77.7)	185 (14.8)	<0.01
NPeT, last	268.7 (53.9)	200.2 (23.3)	<0.01
TPeT, last	250.6 (78.7)	179.8 (15.9)	<0.01

DRIL: Disorganization of retinal inner layers; BCVA: Best corrected visual acuity; RT: Reference time; FT: Foveal thickness; NPaT: Nasal parafoveal thickness; TPaT: Temporal parafoveal thickness; NPeT: Nasal perifoveal thickness; TPeT: Temporal perifoveal thickness. [a]Mann-Whitney *U* test or *t*-test according to the normality test results.

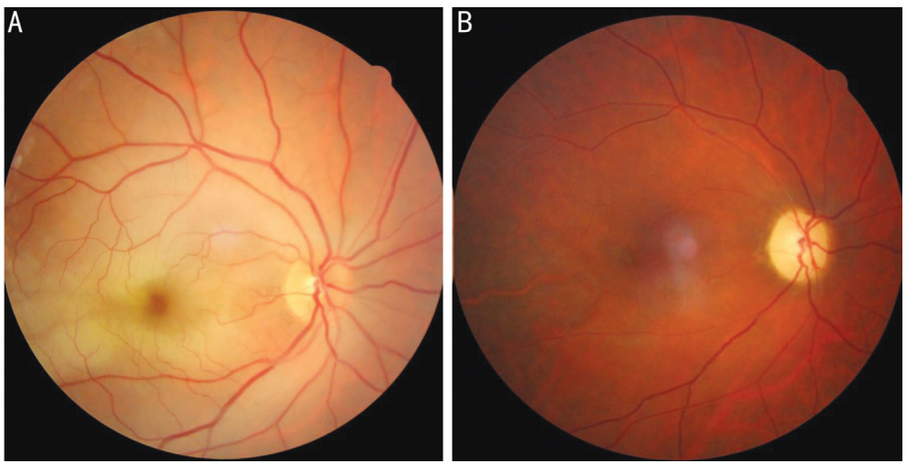

Figure 2 Fundus appearances of a CRAO patient A: First day fundus photo of a CRAO patient; B: Same patient's fundus photo after 2mo. Arterial thinning developed, foveal light refleks disappeared and optic disc seems pale. This patient's right eye's VA is counting fingers.

points), MTC and DRIL score were analyzed as prognostic factors. The correlations between these prognostic factors and visual function were investigated.

In this study we saw that age is not related to visual prognosis. But there was a positive correlation between the RT and final BCVA (Pearson's correlation test, r=0.522) and a negative correlation with the difference of BCVAs (Pearson's correlation test, r=-0.464). The study published in 2004, showed that the retina is irreversibly damaged by acute ischaemia of 4 hours after total occlusion[7]. In practice not every CRAO is totally occluded. That means shorter RT, better VA. This result was similar to studies of Cope *et al*[8] and Beiran *et al*[9]. If we had put some limitations to RT (like maximum 12h) or while we made the statistics, if we had grouped the subjects according to the RT, we would have some much significant findings. However, such a grouping is not preferred because it reduces the number of cases.

Ahn *et al*[10], who studied that whether MT is a prognostic factor, expressed that final central MT is correlated with severe vision loss. Chen *et al*[2] analyzed the relation between MTC and visual functions, and they expressed that MTC is very important about visual prognosis. We also found out in our study that MT and visual functions have a close relationship, especially the correlations between visual functions with nasal MTs were statistically more significant than with temporal MTs. Generally, if a subject's first MT is thick, last MT is thin and the difference of MTs is high, it seems unlikely to improve that patients vision. Of course the duration of the retinal artery occlusion and the sensitivity to treatments is also very important in these cases.

The other parameter that we invastigated as a prognostic factor was DRIL. There were no data about DRIL in retinal arterial oclusions until today. DRIL was first evaluated in terms of visual prognosis in retinal vein occlusions following diabetic patients and was found to be prognostically significant[3-5,11-14]. In Nicholson *et al*'s[5] study, DRIL showed 85% sensitivity and 100% specificity in capillary non-perfusion detection. Grewal *et al*[15] studied DRIL in patients with uveitic macular edema and found out that DRIL is a easily obtained marker of VA for current or resolved uveitic macular edema patients. DRIL scoring has been found to be very important for predicting visual prognosis in patients with idiopathic epiretinal membrane[16]. Guo *et al*[17] investigated structural changes associated with VA in patients with idiopathic macular telangiectasia type 1 using multimodal imaging modalities and found that DRIL may be an important biomarker of predicting VA. An OCT angiography study published in 2018 by Onishy *et al*[18] showed DRIL is associated with multilevel retinal capillary non-perfusion. Another study with OCT angiography also concluded with the same results[19]. The pathogenesis of macular swelling in diabetic, uveitic, retinal venous occlusion and idiopathic epiretinal membrane patients is very different than CRAO patients but DRIL's pathogenesis is the same; capillary non-perfusion and ischemia. It is inevitable that the DRIL which is caused by capillary non-perfusion could be also caused by retinal arterial occlusions. High DRIL scores could be predicted when especially with prolonged elapsed time after the onset of the symptoms. As predicted the DRIL score increased as the RT increased (Pearson's correlation test, r=0.482). We found out that DRIL score has a positive correlation with the final BCVA (Pearson's correlation test, r=0.787) and a negative correlation with the difference of BCVAs in CRAO patients (Pearson's correlation test, r= -0.763). When we investigated the relations of DRIL with other prognostic factors we saw that DRIL has close relationship with RT, MT and MTC. There was a positive correlations between DRIL score and first MTs and a negative correlation with last MTs.

In our study, after all patients' DRIL scores were determined, according to the DRIL score we evaluated patients in 2 separate

groups (DRIL-A and DRIL-B). The patients in the DRIL-A (DRIL score 0-3) group had shorter RT (*t*-test, $P<0.05$), thinner first MTs (Mann-Whitney *U* test, $P<0.01$,except first TPeT), and thicker last MTs (Mann-Whitney *U* test, $P<0.01$, except last FT). As we expressed before, short RT, thin first MT, and thick last MT refers to good prognosis. As a result DRIL-A group had better prognosis with better final BCVA and higher difference of BCVAs compared to DRIL-B group.

We didn't have any control group for the treatment algorythm to understand the role of HBOT for CRAO, but in the lights of previus studies, HBOT seems to be a good choise for treatment if the right conditions are provided[8-9,20]. DRIL score was also correlated negatively with HBOT sessions count (Pearson's correlation test, $r=-0.341$). We think the reason for this was the treatment respond was better for the patients with low DRIL scores, so the increasing VA functions caused the increasing HBOT sessions, so DRIL can be a good guidance for treatment.

Like diabetic rethinopathy, retinal vein occlusions and uveitic macular edema, the DRIL for CRAO patients in the acute phase, could be valuable in terms of visual prognosis, but further studies with larger samples and subgroups are needed to validate this observation.

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Conflicts of Interest: Yilmaz H, None; **Durukan AH,** None.

REFERENCES

1 Hayreh SS, Zimmerman MB. Central retinal artery occlusion: visual outcome. *Am J Ophthalmol* 2005;140(3):376-391.

2 Chen SN, Hwang JF, Chen YT. Macular thickness measurements in central retinal artery occlusion by optical coherence tomography. *Retina* 2011;31(4):730-737.

3 Sun JK, Lin MM, Lammer J, Prager S, Sarangi R, Silva PS, Aiello LP. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. *JAMA Ophthalmol* 2014;132(11):1309-1316.

4 Das R, Spence G, Hogg RE, Stevenson M, Chakravarthy U. Disorganization of inner retina and outer retinal morphology in diabetic macular edema. *JAMA Ophthalmol* 2018;136(2):202-208.

5 Nicholson L, Ramu J, Triantafyllopoulou I, Patrao NV, Comyn O, Hykin P, Sivaprasad S. Diagnostic accuracy of disorganization of the retinal inner layers in detecting macular capillary non-perfusion in diabetic retinopathy. *Clin Exp Ophthalmol* 2015;43(8):735-741.

6 Lange C, Feltgen N, Junker B, Schulze-Bonsel K, Bach M. Resolving the clinical acuity categories "hand motion" and "counting fingers" using the Freiburg Visual Acuity Test (FrACT). *Graefes Arch Clin Exp Ophthalmol* 2009;247(1):137-142.

7 Hayreh SS, Zimmerman MB, Kimura A, Sanon A. Central retinal artery occlusion. Retinal survival time. *Exp Eye Res* 2004;78(3):723-736.

8 Cope A, Eggert JV, O'Brien E. Retinal artery occlusion: visual outcome after treatment with hyperbaric oxygen. *Diving Hyperb Med* 2011;41(3):135-138.

9 Beiran I, Goldenberg I, Adir Y, Tamir A, Shupak A, Miller B. Early hyperbaric oxygen therapy for retinal artery occlusion. *Eur J Ophthalmol* 2001;11(4):345-350.

10 Ahn SJ, Woo SJ, Park KH, Jung C, Hong JH, Han MK. Retinal and choroidal changes and visual outcome in central retinal artery occlusion: an optical coherence tomography study. *Am J Ophthalmol* 2015;159(4):667-676.

11 Radwan SH, Soliman AZ, Tokarev J, Zhang L, van Kuijk FJ, Koozekanani DD. Association of disorganization of retinal inner layers with vision after resolution of center-involved diabetic macular edema. *JAMA Ophthalmol* 2015;133(7):820-825.

12 Mimouni M, Segev O, Dori D, Geffen N, Flores V, Segal O. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with macular edema secondary to vein occlusion. *Am J Ophthalmol* 2017;182:160-167.

13 Berry D, Thomas AS, Fekrat S, Grewal DS. Association of disorganization of retinal inner layers with ischemic index and visual acuity in central retinal vein occlusion. *Ophthalmol Retina* 2018;2(11):1125-1132.

14 Eldeeb M, Chan EW, Sun V, Chen JC. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with macular edema secondary to vein occlusion. *Am J Ophthalmol* 2018;186:167-168.

15 Grewal DS, O'Sullivan ML, Kron M, Jaffe GJ. Association of disorganization of retinal inner layers with visual acuity in eyes with uveitic cystoid macular edema. *Am J Ophthalmol* 2017;177:116-125.

16 Zur D, Iglicki M, Feldinger L, Schwartz S, Goldstein M, Loewenstein A, Barak A. Disorganization of retinal inner layers as a biomarker for idiopathic epiretinal membrane after macular surgery-the DREAM study. *Am J Ophthalmol* 2018;196:129-135.

17 Guo JL, Tang WY, Ye XF, Wu HX, Xu GZ, Liu W, Zhang YJ. Predictive multi-imaging biomarkers relevant for visual acuity in idiopathic macular telangiectasis type 1. *BMC Ophthalmol* 2018;18(1):69.

18 Onishi AC, Ashraf M, Soetikno BT, Fawzi AA. Multilevel ischemia in disorganization of the retinal inner layers on projection-resolved optical coherence tomography angiography. *Retina* 2018.

19 Moein HR, Novais EA, Rebhun CB, Cole ED, Louzada RN, Witkin AJ, Baumal CR, Duker JS, Waheed NK. Optical coherence tomography angiography to detect macular capillary ischemia in patients with inner retinal changes after resolved diabetic macular edema. *Retina* 2018;38(12):2277-2284.

20 Butler FK Jr, Hagan C, Murphy-Lavoie H. Hyperbaric oxygen therapy and the eye. *Undersea Hyperb Med* 2008;35(5):333-387.