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Efficacy and safety of hyperbaric oxygen therapy monitored by fluorescein angiography in patients with retinal artery occlusion

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ABSTRACT

Aims To assess the efficacy and safety of a standardised hyperbaric oxygen therapy protocol (HBOT) monitored by fluorescein angiography (FA) in patients with retinal artery occlusion (RAO).

Methods It is a prospective, non-comparative, monocentric study conducted between July 2016 and March 2022. All consecutive patients diagnosed with RAO within 7 days underwent visual acuity measurement, FA, macular optical coherence tomography (OCT) and OCT-angiography. They received two daily HBOT sessions (2.5 atmosphere absolute, 90 min) until revascularisation assessed by FA. Complete ophthalmic follow-up was scheduled at day 14, day 21 and at 1 month. The main outcome measure was a best-corrected visual acuity (BCVA) improvement defined as a decrease ≥0.3 logMAR at 1 month.

Results Thirty-one patients were included and received a mean number of 33.9 (13–56) HBOT sessions. Retinal revascularisation was observed in 48.4% and 87.1% of patients at days 14 and 21, respectively. The mean BCVA on referral and at 1 month was 1.51 logMAR and 1.10 logMAR, respectively. Fifteen (48.4%) patients achieved the main outcome measure. Six (19.4%) patients experienced minor barotrauma that did not require HBOT discontinuation. The univariate analysis showed that antiplatelet-treated patients (p=0.044) and patients with a poor initial BCVA (p=0.008) were more likely to achieve a BCVA improvement. OCT-angiography was not sensitive enough to diagnose RAO or assess revascularisation.

Conclusion In RAO patients monitored by FA until spontaneous revascularisation of the central retinal artery, HBOT was effective and safe.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Retinal artery occlusion (RAO) is a severe ophthalmic disease characterised by a dramatic decrease in best-corrected visual acuity. Many treatments have been tempted, but none of them has been shown to be both effective and safe.

WHAT THIS STUDY ADDS

⇒ Hyperbaric oxygen therapy (HBOT), administered twice daily until revascularisation of the central retinal artery monitored by fluorescein angiography, was safe and allowed visual acuity improvement (defined as a gain ≥0.3 logMAR) in 48.4% of patients presenting with RAO, despite late referral (up to 7 days after the onset of symptoms).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Eligible patients presenting with RAO should benefit from prompt HBOT whenever possible to maximise visual acuity gain.

INTRODUCTION

Retinal artery occlusion (RAO) is a rare but extremely severe ophthalmic disease characterised by sudden, unilateral, painless visual and/or visual field loss.[1 2] The best-corrected visual acuity (BCVA) is often dramatically decreased.

Depending on the blockade location, RAO is called central retinal artery occlusion (CRAO), branch retinal artery occlusion (BRAO) or cilioretinal artery occlusion.[3] In about 25% of cases, a cilioretinal artery arises from the ciliary arteries and allows vascularisation of part of the macula.[1 4]

Although revascularisation usually occurs spontaneously a few weeks after RAO, the visual prognosis remains poor, which is explained by the terminal and non-anastomotic retinal vasculature and the duration of the occlusion.[3] In their study, Hayreh *et al* showed irreversible retinal damages in CRAO after 240 min of occlusion,[5] but a large number of studies suggest that visual improvement in humans still possible after much longer periods, raising the question of interindividual variability.

Many treatments have been tempted in RAO, such as carbogen inhalation, ocular massage, hypotensive eyedrops,[6 7] oral and intravenous acetazolamide,[6] systemic steroids, antiplatelets,[8] neodymium:yttrium-aluminium-garnet laser,[9] intra-arterial fibrinolysis (IAF),[6 10] anterior chamber paracentesis[11] or pars plana vitrectomy with removal of the embolus. However, none of these treatments has been shown to be both effective and safe and there is currently no standard of care for treating RAO.

Since 1965, several studies have assessed hyperbaric oxygen therapy (HBOT) for the treatment of RAO.[12] HBOT aims to improve oxygen transport and diffusion. HBOT increases plasma oxygen concentrations and induces an up to 23-fold increase in the amount of oxygen dissolved in the plasma.[13] Moreover, HBOT is associated with increased hydrostatic pressure and enhanced red

blood cell deformity. Under normoxic conditions, about 15% of the oxygen supply to the retina come from the choroidal circulation that supplies the outer retinal layers.[13] Taken together, these data indicate that HBOT may allow oxygen diffusion into the inner retinal layers through the choroidal vessels and the vitreous body. Several studies have reported favourable outcomes with HBOT (ie, an improvement compared with the natural course of RAO) without major adverse events (AEs).[7 14–18] However, these studies had several limitations such as a small sample size, a lack of standardised HBOT protocol, a subjective main outcome measure and several other confounding factors. To date, there is no consensus on the duration of HBOT and the ideal number of daily sessions.[19] Based on the underlying pathophysiology of RAO and mechanisms of HBOT, we hypothesised that HBOT could allow indirect oxygenation of the inner layers of the ischaemic retina through the choroid and the vitreous body until spontaneous revascularisation takes place. Fluorescein angiography (FA) remains the gold standard to assess RAO and subsequent revascularisation.[1] Recently, non-invasive optical coherence tomography-angiography (OCT-A) has gained interest and several small studies have investigated its interest in RAO.[20]

The primary aim of this study was to investigate the efficacy of a standardised HBOT protocol monitored by repeated FA for treating RAO. The secondary aims were to determine the related prognosis factors, the safety of the HBOT protocol, and whether non-invasive OCT-A could be an alternative to FA to assess RAO and revascularisation.

MATERIAL AND METHODS

Study design

A prospective monocentric study was conducted in Nice University Hospital between July 2016 and March 2022. All the patients referred to our ophthalmologic emergency department for RAO were screened. The diagnosis of RAO was made by an ophthalmologist based on the clinical examination and FA findings.

Inclusion and exclusion criteria

All patients with CRAO or BRAO for less than 7 days were included in the study. Patients with cilioretinal artery occlusion, CRAO with preserved cilioretinal artery or CRAO associated with vein occlusion were excluded from the study. Other exclusion criteria were: patients with a contraindication to HBOT (acute sinusitis, ear disease, pulmonary disorder such as recent pneumothorax or emphysema, claustrophobia), who did not receive at least 10 HBOT sessions, with concomitant cerebral stroke or significant internal carotid stenosis assessed by contrast-enhanced cervical and cerebral CT scan (HBOT discontinuation), with fluorescein allergy, and with any history of previous RAO treatment.

Study protocol

The initial ophthalmological assessment included: BCVA, intraocular pressure, slit-lamp examination, fundus examination, macular OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany), FA and OCT-A (AngioVue, Optovue, California, USA). At the end of the ophthalmological assessment, the patients who met the inclusion criteria were immediately referred to the HBOT department. A complete clinical examination and an ECG were performed and a blood sample was taken to rule out any cardiac abnormality, artery aetiology (eg, Horton vasculitis) or any contraindication to HBOT.[21] The patients underwent their first 90 min HBOT session at 2.5 absolute atmosphere (ATA) in a HAUX Comex hyperbaric chamber. After the session, patients were referred to the radiology department to undergo contrast-enhanced cervical and cerebral CT-scan to rule out any cerebral stroke or internal carotid dissection. In case of concomitant cerebral stroke or significant internal carotid stenosis, patients were withdrawn from the protocol and hospitalised in the neurovascular department. If contrast-enhanced CT scan was unremarkable, the patients received two daily 90 min HBOT sessions for 15 days in an outpatient basis. At day 15, a new ophthalmological examination was performed, similar to that performed on referral. Retinal revascularisation was assessed by FA. In case of retinal reperfusion, HBOT was discontinued, and a final ophthalmological follow-up was scheduled at day 30. Otherwise, HBOT was continued with two daily sessions and FA was repeated on day 21. In case of retinal ischaemic areas seen on FA at day 21, panretinal photocoagulation was performed. All patients were seen at day 30 for the final ophthalmological examination.

In this study, on FA, RAO was defined as an incomplete filling of retinal arterial vessels 30 s after fluorescein injection.[22] On OCT-A, the vessel density (VD) of the superficial capillary plexus was also recorded and automatically segmented by the software. We choose to monitor the superficial capillary plexus based on the findings provided by Yu *et al*.[23 24]

The main outcome measure was a BCVA improvement, defined as a decrease ≥0.3 logMAR at 1 month.[1 7 25] The secondary outcome measures were HBOT-related AEs and the sensitivity of OCT-A to assess retinal artery revascularisation compared with FA.

Statistics

Descriptive statistics are presented as numbers and percentages for categorial variables and as means±SDs for continuous variables. Analyses were performed by using χ^2 and Student's t-tests to compare qualitative and quantitative data, respectively. SPSS software V.25 (IBM) was used and a $p<0.05$ was considered statistically significant.

RESULTS

Among the 74 patients diagnosed with RAO over the study period, 31 patients with a mean age of 68.3 (15–93) years met the inclusion criteria and were included (table 1). Most excluded patients did not undergo a complete ophthalmological examination (FA, OCT-A) on referral or during the follow-up. A female predominance (n=19, 61.3%) was noted. CRAO and BRAO were diagnosed in 19 (61.3%) and 12 (38.7%) patients, respectively. Anticoagulants and antiplatelets were taken by 4 (12.9%) and 9 (29.0%) patients, respectively. The aetiology of RAO was identified in 20 (64.5%) patients: embolic heart disease in 4 (12.9%) patients, significative carotid stenosis in 2 (6.5%), non-significative carotid stenosis in 11 (35.4%) patients and iatrogenic occlusion following arterial embolisation in 3 (9.7%) patients.

The mean BCVA on referral was 1.51 (0–2.6) logMAR (or approximately 20/600 in Snellen chart) (table 2). At the end of the HBOT protocol, the mean BCVA was 1.1 (0–2.6) logMAR (logarithm of the minimum angle of resolution) (20/250 in Snellen chart). Fifteen (48.4%) patients achieved the main outcome measure defined as an improvement ≥0.3 logMAR. The subgroup analysis showed a better BCVA improvement in CRAO patients (52.6%) compared with BRAO patients (41.6%).

Retinal revascularisation assessed by FA occurred in 48.4% of patients at day 14 and in an additional 38.7% of patients at

Table 1 Patients' baseline characteristics

Patients' characteristics	No (%)	Mean (range)
Male	12 (38.7)	
Female	19 (61.3)	
Age (years)		68.3 (15-93)
Smoking status		
Yes	5 (16.1)	
No	12 (38.7)	
NA	14 (45.2)	
High blood pressure		
Yes	16 (51.6)	
No	15 (48.4)	
Dyslipidaemia		
Yes	6 (19.4)	
No	25 (80.6)	
Diabetes		
Yes	1 (3.2)	
No	30 (96.8)	
Anticoagulants		
Yes	4 (12.9)	
No	27 (87.1)	
Antiplatelets		
Yes	9 (29.0)	
No	22 (71.0)	
Type of retinal occlusion		
CRAO	19 (61.3)	
BRAO	12 (38.7)	
Aetiology of RAO		
Embolic heart disease	4 (12.9)	
Significative carotid stenosis	2 (6.4)	
Non-significative carotid stenosis	11 (35.4)	
Not determined	11 (35.4)	
Other	3 (9.7)	

BRAO, branch retinal artery occlusion; CRAO, central retinal artery occlusion; NA, not available; RAO, retinal artery occlusion.

1 month (table 3). Only four (12.9%) patients did not achieve retinal revascularisation at month one. These patients were all treated with panretinal photocoagulation. The time between the first ocular symptoms and the first HBOT session was <12 hours in 10 (32.3%) patients. Patients received a mean number of 33.9 (13–56) hyperbaric sessions. All patients received two daily HBOT sessions except three patients who only received one daily session between 17 March 2020 and 20 April 2020 due to the COVID-19 lockdown. A SBP (systolic blood pressure) ≥160 mm Hg was diagnosed during HBOT sessions in 9 (29%) patients for which antihypertensive agents were required. Six (19.4%) patients experienced minor barotrauma for which HBOT discontinuation was not required.

Table 3 Results of the secondary outcome measures

	No (%)	Mean (range)
BCVA improvement≥0.1 logMAR	16 (51.6)	
Revascularisation seen on ocular angiography		
Day 14	15 (48.4)	
Day 21	27 (87.1)	
No revascularisation	4 (12.9)	
Treatment initiated (anticoagulant or antiplatelet)		
Yes	7 (22.6)	
No	10 (32.3)	
NA	14 (45.2)	
Concomitant stroke revealed on CT scan		
Yes	0 (0)	
No	31 (100)	
Time between the ocular symptoms and the first HBOT session		
<12 hours	10 (32.3)	
>12 hours	21 (67.7)	
Time between the referral to the hyperbaric department and the first hyperbaric session		
<1 hour	28 (90.3)	
>1 hour	3 (9.7)	
HBOT-induced barotrauma		
Yes	6 (19.4)	
No	25 (80.6)	
Arterial hypertension during HBOT session		
Yes	9 (29.0)	
No	22 (71.0)	
Hyperbaric session regimen		
Once daily	3 (9.7)	
Twice daily	28 (90.3)	
OCT		
CMT at day 0		342.8 (243–800)
CMT at day 30		280.8 (225–508)
p value		p=0.009
EDI-OCT		
SCT at day 0		228.0 (117–400)
SCT at day 30		214.9 (103–357)
P value		p=0.560
OCT-angiography		
VD at day 0		40.5 (36.6–49.5)
VD at day 30		41.6 (36–48.1)
P value		p=0.905

BCVA, best-corrected visual acuity; CMT, central macular thickness; EDI, enhanced depth imaging; HBOT, hyperbaric oxygen therapy; logMAR, logarithm of the minimum angle of resolution; OCT, optical coherence tomography; SCT, subfoveal choroidal thickness; VD, vessel density.

The mean CMT assessed on OCT on referral was 342.8 (243–800) μm in the affected eye and was significantly reduced to 280.8 (225–508) μm at 1 month (p=0.009). The mean SCT was

Table 2 Results of the main outcome measure

	No of patients	Baseline BCVA (range)	BCVA at 1 month (range)	No of patients (%) with BCVA improvement ≥0.3 logMAR (logarithm of the minimum angle of resolution)
All patients	31	1.51 (0–2.6)	1.10 (0–2.6)	15 (48.4)
CRAO patients	19	1.93 (0.4–2.6)	1.52 (0–2.6)	10 (52.6)
BRAO patients	12	0.86 (0–2.6)	0.53 (0–2.3)	5 (41.6)

BRAO, branch retinal artery occlusion; CRAO, central retinal artery occlusion;

Table 4 Prognostic factors associated with the main outcome measure (BCVA decrease≥0.3 logMAR) for all patients (CRAO+BRAO)

Visual acuity decrease≥0.3 logMAR	P value
CRAO	0.551
BRAO	0.551
High blood pressure	0.578
Dyslipidaemia	0.185
Diabetes	0.548
Anticoagulants on referral	0.622
Antiplatelets on referral	0.044
Aetiology:	
Embolic heart disease	0.576
Carotid stenosis	1.000
High blood pressure on referral to the hyperbaric department	0.693
Hypertension during the first hyperbaric session	1.000
First hyperbaric session <12 hours after onset of symptoms	1.000
HBOT initiated during the first hour of arrival at the hyperbaric oxygen department	0.232
Barotrauma	0.920
Twice daily sessions	0.232
No of hyperbaric sessions	0.488
Treatment initiated (antiplatelet or anticoagulant)	0.587
BCVA on referral	**0.008**
Revascularisation at day 14	1.000
Revascularisation at day 21	0.607
CMT on referral	0.798
CMT at day 30	0.905
SCT on referral on EDI	0.598
SCT at day 30 on EDI	0.931
VD on referral on OCT-A	0.560
VD at day 30 on OCT-A	0.242

BCVA, best-corrected visual acuity; BRAO, branch retinal artery occlusion; CMT, central macular thickness; CRAO, central retinal artery occlusion; EDI, enhanced depth imaging; HBOT, hyperbaric oxygen therapy; logMAR, Logarithm of the Minimum Angle of Resolution; OCT-A, optical coherence tomography-angiography; SCT, subfoveal choroidal thickness; VD, vessel density.

228.0 (117–400) μm and 214.9 (103–357) μm on referral and at 1 month, respectively (p=0.560). The mean SCT on referral was 212.4 µm and 246.5 µm, respectively, in patients who achieved a BCVA improvement and in those who did not (p=0.620).

The univariate analyses showed that patients treated with antiplatelets before RAO (p=0.044) and patients with a poor initial BCVA (p=0.008) were more likely to achieve the main outcome measure (table 4).

Seventeen (54.8%) patients were not assessed by OCT-A on referral and during the follow-up because of excessive blinking, motion artefacts, or low-quality images. On referral, mean VD in superficial capillary plexus was 40.5%. It was 41.6% at 1 month and there was no significative improvement (p=0.905). OCT-A findings always show a normal filling of the main arterial trunks even when FA showed occlusion at 1 day (31 patients) and at 1 month (4 patients). However, OCT-A shows capillary defects in all patients on referral and 71.4% of the patients at 1 month. Defects on OCT-A where not always associated with defects in FA.

DISCUSSION

In this study, we investigated the efficacy and safety of a standardised HBOT protocol monitored by FA in patients with RAO. A BCVA improvement, defined as a gain ≥0.3 logMAR, was found in 48.4%, 52.6% and 41.6% of RAO, CRAO and BRAO patients, respectively. The use of antiplatelets and a poor initial BCVA were significantly associated with a gain ≥0.3 logMAR. No serious AEs required HBOT discontinuation.

Our results are in accordance with previous studies in which HBOT was used to treat RAO (table 5).[7 14 15 19] In their retrospective comparative study, Beiran *et al* have found that 82.9% of patients treated with HBOT achieved a BCVA improvement compared with 29.7% in the untreated group (table 5).[14] Their results were better than ours and this could be explained by the inclusion of patients with RAO for <8 hours.[14] Weinberger *et al* have reported a visual improvement in 90.5% of patients but this result could be explained by a different and non-widely recognised primary outcome measure (colour vision and visual field).[15] By contrast, only 29% of patients achieved a visual improvement in the study by Elder *et al* but they only received a mean number of four HBOT sessions.[17] These results highlight the lack of consensus on the ideal HBOT protocol (total number of sessions, number of daily sessions). HBOT is thought to oxygenate the inner retinal layers through a passive diffusion from the underlying choroid and vitreous body.[13 26 27] Based on this underlying pathophysiology, we decided to continue HBOT until revascularisation of the central retinal artery. To the best of our knowledge, our study was the first to assess HBOT duration by assessing central retinal artery revascularisation on FA. We chose to perform two daily sessions based on the recommendations provided by the European Consensus Conference on Hyperbaric Medicine.[13] We hypothesised that two daily sessions had the advantages to provide (1) an immediate oxygenation of the retina via the choroidal vasculature and (2) a progressive retinal oxygenation through the vitreous body that could be considered as an oxygen reservoir allowing a slow and progressive release of the accumulated oxygen.[26 28] In their studies, Beiran *et al* and Hadanny *et al* have performed two daily hyperbaric sessions during the first 3 days and a daily session thereafter.[7 14] To date, no study has shown the superiority of a protocol over another. HBOT is thought to promote arterial vasoconstriction that should be avoided in RAO. Therefore, we chose a protocol at 2.5 ATA that is known to reverse the vasoconstriction reflex as recommended by the European Consensus Conference on Hyperbaric Medicine based on Saltzman's work.[29] Moreover, Kawamura *et al* have failed to find any arterial vasoconstriction of the hypoxaemic tissues under highly oxygenated arterial conditions.[30] We assumed that the high number of sessions and the use of two daily sessions could explain why our results are similar to those of previous studies (table 5) despite the inclusion of patients with symptoms for >12 hours (about two-thirds of our patients).

No serious AEs occurred over the study period. Of the 31 patients included, 6 (19.4%) experienced minor barotrauma for which HBOT discontinuation was not required. This proportion is higher than previously reported (table 5). Elder *et al* and Hadanny *et al* have reported barotrauma in 3.2% and 2.3% of patients, respectively.[7 17] This result could be explained by the higher number of sessions received (34 sessions) in our study compared with other studies (table 5).

Numerous treatments have been used to achieve early revascularisation. In their meta-analysis, Man *et al* have reported a decrease by ≥0.2 logMAR in 79% of patients treated with transluminal Nd:YAG embolectomy.[9] This proportion is higher than ours, and this could be explained by the use of a different success criterion (0.2 vs 0.3 logMAR). However, as stressed by Hayreh himself, only a BCVA change ≥0.3 logMAR may be considered clinically significant.[1 3 31] Anterior chamber paracentesis has also been assessed by Fieβ *et al* and was associated with a BCVA improvement in 23.7% of cases, a proportion that is similar to the natural course of the disease.[11] Schumacher *et al* have compared IAF and conservative treatment (hemodilution,

Table 5 Summary of the main studies assessing HBOT for treating retinal artery occlusion

Study, year	Current study, 2021	Beiran *et al*, 2001[14]	Weinberger *et al*, 2002[15]	Menzel-Severin *et al*, 2012[16]	Hadanny *et al*, 2016[7]	Elder *et al*, 2017[17]	Wu *et al*, 2018[19]
Study design	Prosp. Non-Comp.	Retrosp. Comp.	Prosp. Non-Comp.	Retrosp. Comp.	Restrosp. Non-Comp.	Restrosp. Non-Comp.	Meta-analysis
Treatment	HBOT	HBOT vs Observ.	HBOT+HD	HBOT+HD vs. HD	HBOT	HBOT	HBOT
No of patients	31	72	21	80	128	31	251
Inclusion criteria	CRAO+BRAO for <7 days	CRAO+BRAO for <8 hours	CRAO for <12 hours	CRAO for<12 hour with BCVA<+1 logMAR	CRAO for<20 hour with BCVA<0.5 logMAR	CRAO+BRAO	CRAO+BRAO
Mean age (years)	68.3	69.5 vs 56	NR	69 vs 74	66.4	70	NR
Mean initial BCVA (logMAR)	+1.51	+1 vs. +1.1	+2.3 to +1.1	+1.8 vs +1.7	+2.14	+2.3 to +0.2	NR
Mean final BCVA (logMAR)	+1.1	+0.5 vs. +0.9	NR	+1.5 vs +1.6	+1.62	+2.6 to −0.1	NR
Success criteria	Improv. ≥0.3 logMAR	Improv. ≥3 Snellen lines	Subjective visual improv.	Improv. ≥3 Snellen lines	Improv. ≥0.3 logMAR	NR	NR
Visual improv. according to the success criterion (%)	48.4	82.9 vs 29.7 p=0.000	90.5	38.8 vs 17.9 p=0.06	67.2	29	ten to 90 OR 5.61 (3.6–8.73)
Good prognosis factors	Antiplatelets on referral	High blood pressure	NR	Aspirin	No cherry red spot	Time to treatment	Duration of HBOT
Mean no of HBOT sessions	34	NR	NR	5	4	4	NR
HBOT-related adverse events (%)	Barotrauma (19.4) Hypertension during the session (29.0)	NR	NR	None	Barotrauma (2.3) Otalgia (1.5) Epistaxis (0.7) Dyspnoea (0.7)	Claustrophobia, barotrauma, acute upper respiratory tract infection	NR

BRAO, branch retinal artery occlusion; Comp, comparative; CRAO, central retinal artery occlusion; HBOT, hyperbaric oxygen therapy; HD, haemodilution; logMAR, Logarithm of the Minimum Angle of Resolution; NR, not reported; Observ, observation; Prosp, prospective; RAO, retinal artery occlusion; Retrosp, retrospective; VA, visual acuity.

ocular massage, acetazolamide) in a multicentric randomised clinical trial.[6] They have found an improvement by ≥0.3 logMAR in 57.1% of patients in the IAF group vs 60% in the conservative group. However, due to a significantly higher rate of AEs in the IAF group, the study was prematurely stopped after the first interim analysis.

However, before considering HBOT as an effective treatment for RAO, it is also essential to compare our results with the natural course of the disease. Our study was not comparative (we did not compare HBOT to the natural evolution of the disease without any treatment) because (1) RAO is rare (1–2 cases per month), (2) the natural evolution of RAO is well known and has been widely reported in large studies, (3) there is no standard of care for treating RAO and (4) the current literature reports favourable efficacy and safety profiles of HBOT. Hayreh and Zimmerman have extensively described the natural course of RAOs.[3] When considering the four CRAO subtypes (non-arteritic, transient non-arteritic, arteritic and non-arteric with cilioretinal artery) seen during the 7 days of the onset of symptoms with a visual acuity <20/40, a BCVA improvement (≥0.3 logMAR) was achieved by 38 out of 99 patients (38.4%). In our study, 26 patients had a visual acuity <20/40 and 57.7% of them achieved a BCVA improvement ≥0.3 logMAR. When considering only non-arteritic CRAO patients seen during the 7 days of the onset of symptoms and with a visual acuity of counting fingers or worse, Hayreh *et al* have reported a BCVA improvement in 22% of patients. Using the same inclusion criteria, 58.8% of our patients achieved a BCVA improvement (table 6). Beiran *et al* have confirmed these results in their study with a BCVA improvement achieved by 82.9% and 29.7% of patients treated with HBOT and observation alone, respectively.[14] However, their study had a retrospective design and despite favourable outcomes reported in a recent meta-analysis,[19] there is currently no ongoing prospective randomised study comparing HBOT and observation alone.

In our study, we found an association between the use of antiplatelets on referral and a better visual improvement (p=0.044). Although not recognised as a standard of care for CRAO, antiplatelets are widely prescribed for the secondary prevention of cardiovascular events. Here, we hypothesised that the use of antiplatelets could be associated with a smaller thrombus size, thus allowing better residual arterial flow and hyperbaric oxygenation of the inner retinal layers. Surprisingly, the time between the onset of the first symptoms and HBOT initiation was not associated with a BCVA improvement (p=1.000), unlike the results reported by Elder *et al* and Ilbasmis *et al*.[17 18] Previous animal studies have found that retinal damage occurred as early as 97 min after retinal occlusion.[5] No human data are currently available. We hypothesised that, as with ischaemic cerebral strokes, several ischaemic retinal cells could be in a state of hypoxic penumbra and stimulated by late treatments such as HBOT. This explains why patients with RAO for 7 days were included in our study. The SCT measured on EDI-OCT was not associated with a better visual prognosis. We initially

Table 6 Comparison of the study by Hayreh and Zimmerman[3] and our study in terms of CRAO patients with a visual acuity of counting fingers or worse

Study	Study design	No of patients	Mean age (years)	Treatment	BCVA on referral (logMAR)	Final VA (logMAR)	% of patients with BCVA improvement ≥0.3 logMAR
Hayreh and Zimmerman, 2005[3]	Prosp. Non-Comp.	58	67.7	Observation	≤+1.7	NA	22
Current study	Prosp. Non-Comp.	17	70.1	HBOT	+2.1 (mean)	+1.6 (mean)	58.8

BCVA, best-corrected visual acuity; Comp, comparative; CRAO, central retinal artery occlusion; HBOT, hyperbaric oxygen therapy; logMAR, Logarithm of the Minimum Angle of Resolution; NA, not applicable; Prosp, prospective.

hypothesised that a greater SCT could be a favourable prognosis factor by enhancing oxygen diffusion through the choroidal vasculature.

In this study, we also aimed to investigate whether OCT-A could be an alternative to FA to assess retinal occlusion and subsequent revascularisation. Based on FA findings, spontaneous revascularisation occurred in 48.4% and 87.1% of patients at day 14 and day 21, respectively. This result is in accordance with previous studies.[13] Although all OCT-A examinations performed in our study on referral revealed a reduced superficial capillary plexus vascularisation, a persistent retinal blood flow in the main arterial trucks was suspected on OCT-A despite the absence of arterial filling on early and late (2 min) FA. Taken together, these data tended to indicate that the sensitivity of OCT-A was insufficient to assess arterial occlusion on referral as well as the subsequent revascularisation and this finding suggests that FA remains the gold standard allowing a better 'kinetic' assessment of the retinal blood flow compared with the 'frozen' images provided by OCT-A. Even if OCT-A is useless in the diagnosis of CRAO, it brings us some important information. First, we found a persistent main trunk blood flow in 100% of the OCT-A on referral. This can be explained by a minimal persistence of blood circulation not visible in FA, thus justifying the use of HBOT several days after the beginning of symptoms. Second, we also found that OCT-A allowed better visualising small capillary defects at 1 month compared with FA contrary to Bonini Filho *et al*[20] who showed decreased perfusion in superficial plexus corresponding to the areas of delayed perfusion on FA. Thus, with new wild-field OCT-A maybe the PRP should be based on OCT-A findings rather than FA findings. Thirstily, even if VD was not significantly improved at 1 month and was not associated with better visual outcomes in accordance with Yang *et al*,[32] we could think, as in diabetic retinopathy, that this exam could have a prognosis value in CRAO not demonstrated in our study because of the small sample size of our study.

To conclude, HBOT, administered twice daily until revascularisation of the central retinal artery, provides favourable results without major AEs. Monitoring patients with FA to determine HBOT duration allows customising treatment with good results despite late referral up to 7 days after the onset. About half of our patients achieved a significant BCVA improvement (≥0.3 logMAR), a higher proportion than without treatment (natural evolution of the disease). Further larger studies are needed to confirm our findings.

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