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# Efficacy and safety of a standardized hyperbaric oxygen therapy protocol for retinal artery occlusion

Hélène Di Vincenzo-Giraud

► **To cite this version:**

Hélène Di Vincenzo-Giraud. Efficacy and safety of a standardized hyperbaric oxygen therapy protocol for retinal artery occlusion. Human health and pathology. 2020. dumas-02962761

**HAL Id: dumas-02962761**

**<https://dumas.ccsd.cnrs.fr/dumas-02962761>**

Submitted on 9 Oct 2020

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# THESE

POUR L'OBTENTION DU DIPLOME D'ETAT  
DE DOCTEUR EN MEDECINE  
SPECIALITE MEDECINE GENERALE

Présentée et soutenue publiquement par

**Hélène DI VINCENZO épouse GIRAUD, née le 29 Mars 1991 à Colmar**

Le 29 Juin 2020

**EFFICACITE ET PROFIL DE SECURITE D'UN PROTOCOLE STANDARDISE  
D'OXYGENOTHERAPIE HYPERBARE CHEZ LES PATIENTS PRESENTANT  
UNE OCCLUSION ARTERIELLE RÉTINIENNE**

**EFFICACY AND SAFETY OF A STANDARDIZED HYPERBARIC OXYGEN  
THERAPY PROTOCOL FOR RETINAL ARTERY OCCLUSION**

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## REMERCIEMENTS

### **A ma Présidente de Jury, Madame le Professeur Stéphanie BAILLIF**

*Vous me faites l'honneur de présider ce jury et de juger mon travail. Je vous témoigne ma profonde et respectueuse reconnaissance.*

### **A mon Directeur de Thèse, Monsieur le Docteur Arnaud MARTEL**

*Tu as accepté de m'accompagner tout au long de ce travail. Merci pour ton soutien, pour tes encouragements. J'ai beaucoup appris à tes côtés. Je te remercie pour ta patience et tes conseils. Cela a été un plaisir de travailler avec toi.*

### **A Monsieur le Professeur Jacques LEVRAUT**

*Je vous prie de recevoir mes sincères remerciements pour avoir accepté de juger mon travail. Veuillez croire en l'expression de ma respectueuse considération.*

### **A Monsieur de Professeur Associé Gilles GARDON**

*Merci pour le temps que vous passez au service des étudiants, pour nous apporter une formation de qualité, et transmettre combien la médecine générale est une discipline noble et passionnante. Je vous témoigne ma profonde et respectueuse reconnaissance.*

### **A Monsieur le Docteur Andreas KAUERT**

*Vous me faites l'honneur d'apporter votre expérience à la critique de ce travail en siégeant dans mon jury de thèse. La médecine hyperbare est une spécialité qui mérite d'être connue et reconnue. Je vous prie de bien vouloir accepter ma respectueuse considération.*

**A Thomas,**

*Pour toutes ces années où tu m'as soutenue, sans faille. Pour ton amour, ta présence, ton écoute et bien sûr ta patience ! Tu es l'épaule sur laquelle je m'appuie, tu m'es si précieux... Et pour ne rien gâcher, tu es un papa formidable. Merci pour tout, je t'aime.*

**A Olivia,**

*Mon bébé, tu n'as qu'un an mais je suis déjà tellement fière d'être ta maman. Peut être qu'un jour tu seras intéressée par la lecture de ce travail... Mais en attendant, découvre le monde avec ton regard et ton émerveillement de petite fille. Je t'aime plus que tout.*

**A mes parents,**

*Pour votre soutien inconditionnel tout au long du chemin parcouru, pour être toujours là dans les moments qui comptent pour moi, les meilleurs comme les moins bons. C'est grâce à vous si j'en suis là aujourd'hui. Merci pour tout. Je vous aime.*

**A mon frère et ma sœur,**

*Même si nous sommes parfois éloignés, je sais que l'on pense les uns aux autres, et que les liens qui nous unissent sont forts. Merci pour votre soutien tout au long de ces années. Je vous aime.*

**A mes beaux-parents,**

*Vous m'avez accueillie, soutenue et choyée comme votre fille. Je vous en remercie. J'ai trouvé en vous des deuxièmes parents. Vous avez une grande place dans mon cœur. Merci tout particulier à toi Laurence, qui sera probablement la dernière personne à lire ce manuscrit avant qu'il ne parte à l'impression, histoire de vérifier la mise en page pour la 100<sup>ème</sup> fois...*

**A ma famille,**

*Pour votre soutien et votre amour, depuis toujours. Une pensée pour les êtres chers qui, je l'espère, sont fiers de moi depuis là haut...*

***A mes chers confrères et amis,***

*Ninette, PA, Tutu, Clara, Djé, rencontrés sur les bancs de la fac, merci ! Ces années de galère nous ont permis de créer de véritables liens d'amitié ! Merci pour nos francs moments de rigolade, nos soirées mémorables, nos sous colles parfois mouvementées, votre soutien et votre amitié. Toutes ces années m'auraient paru bien longues sans vous !*

***Aux amis non carabins,***

*Manue, Romain, Clairette, Pacs, Pierre, Elo, Thierry...*

*Qui m'offrent un bol d'air frais... et des apéros par Skype ! Ce serait trop long de vouloir résumer tant d'années d'amitié, alors MERCI pout tout.*

***Aux équipes paramédicales,***

*Avec qui j'ai eu le plaisir de travailler tout au long de mes études. Vous m'avez beaucoup appris, surtout sur l'importance du travail d'équipe !*

Et à tous ceux que j'ai oublié, j'espère qu'ils ne m'en tiendront pas rigueur...

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## Première partie : Résumé

# **EFFICACITE ET PROFIL DE SECURITE D'UN PROTOCOLE STANDARDISE D'OXYGENOTHERAPIE HYPERBARE CHEZ LES PATIENTS PRESENTANT UNE OCCLUSION ARTERIELLE RÉTINIENNE**

### Introduction :

L'occlusion de l'artère centrale de la rétine (OACR) est une pathologie vasculaire grave et rare, se traduisant par une perte d'acuité visuelle brutale et indolore. Son incidence est estimée à 8.5 pour 100 000 personnes par an, mais elle peut être plus élevée en raison d'une sous-déclaration. Il n'y a actuellement aucun consensus concernant la prise en charge de l'OACR, et peu de preuves pour soutenir une quelconque modalité de traitement. Malgré une série de cas limitée, l'oxygénothérapie hyperbare (OHB) est recommandée pour traiter l'OACR par la Undersea and Hyperbaric Medical Society (UHMS) et par le Comité européen pour la médecine hyperbare. Notre objectif était d'évaluer l'efficacité, en terme d'acuité visuelle, d'un protocole standardisé de traitement par oxygénothérapie hyperbare (OHB) chez les patients souffrant d'une occlusion de l'artère rétinienne (OAR).

### Matériel et Méthode :

Une étude rétrospective a été menée conjointement dans le service d'Ophtalmologie et dans l'Unité de traitement par Oxygénothérapie hyperbare du Centre Hospitalier Universitaire (CHU) de Nice, de juillet 2016 à septembre 2019. Les patients présentant une OACR ou une occlusion de la branche de l'artère centrale de la rétine (OBACR) depuis moins de sept jours, diagnostiquée par le service des urgences ophtalmologiques, ont été inclus pendant la période d'étude. Le critère de jugement principal était l'amélioration de l'acuité visuelle, définie comme une diminution de 0,3 logMAR à un mois.

Notre protocole d'étude était le suivant : le diagnostic d'OACR ou d'OBACR était établi par un ophtalmologue du CHU de Nice. Une fois le diagnostic confirmé, le patient était immédiatement orienté vers le service d'oxygénothérapie hyperbare, où il bénéficiait de sa première séance au

caisson hyperbare, durant 90 minutes et à une pression de 2.5 ATA. À la fin de la séance, le patient réalisait un scanner cérébral et des troncs supra aortiques afin d'exclure toute dissection ou sténose de la carotide interne et/ou un accident vasculaire cérébral associé. Dès le lendemain, le patient bénéficiait de deux séances quotidiennes d'oxygénothérapie hyperbare (90 min, 2.5 ATA) sept jours sur sept, pendant au moins 15 jours. Au 15<sup>ème</sup> jour, un nouvel examen ophtalmologique était effectué, avec une évaluation de l'acuité visuelle, un fond d'oeil, une tomographie par cohérence optique (OCT) et une angiographie à la fluorescéine. En cas de reperfusion rétinienne constatée par l'angiographie, l'OHB était interrompue. Si aucune perfusion n'était constatée, le traitement était poursuivi pendant une semaine supplémentaire avec un contrôle au 21<sup>ème</sup> jour. La durée maximale du traitement était de 21 jours. Si l'occlusion rétinienne persistait lors de l'angiographie rétinienne au jour 21, une photocoagulation pan rétinienne était effectuée pour éviter d'autres complications ophtalmologiques, notamment le glaucome néovasculaire.

Les analyses statistiques ont été réalisées à l'aide du test exact de Fisher et des tests de Mann-Whitney pour comparer les données qualitatives et quantitatives respectivement. Le logiciel SPSS (IBM, Chicago, Illinois) a été utilisé et une valeur  $p < 0,05$  a été considérée comme statistiquement significative.

### Résultats :

Vingt-huit patients ont été inclus pendant la période d'étude. La moyenne de l'acuité visuelle (AV) initiale était de 1.5 logMAR (0-2.3). A l'issue du protocole d'OHB, l'AV moyenne était de 0.9 logMAR (0-2.3) et était statistiquement améliorée ( $p=0.001$ ). Dans le sous-groupe de patients atteints d'occlusion de l'artère centrale de la rétine (OACR), l'AV moyenne au départ était de 1.9 logMAR (0.1-2.6). À un mois, elle était de 1.4 logMAR (0-2.3) et était également statistiquement améliorée ( $p=0.013$ ).

L'analyse univariée a identifié l'hypertension artérielle ( $p=0.008$ ), la dyslipidémie ( $p=0.038$ ), le traitement antiplaquettaire ( $p=0.033$ ) et une faible AV initiale ( $p=0.001$ ) comme facteurs pronostic péjoratifs. Le fait de subir un barotraumatisme pendant une séance d'oxygénothérapie hyperbare a été associé à un meilleur pronostic ( $p=0.036$ ). Dans l'analyse multivariée, seules l'hypertension artérielle ( $p=0.039$ ) et la faible valeur initiale de l'AV ( $p=0.005$ ) étaient associées à un mauvais pronostic.

Dans le sous-groupe de patients atteints d'OACR (n=15), le diabète (p=0.042) et la cardiopathie embolique (p=0.049) ont été associés à un mauvais pronostic dans l'analyse univariée, alors que la prise en charge initiale rapide (p=0.042) et les séances bi quotidiennes d'oxygénothérapie hyperbare (p=0.032) se sont révélées être des facteurs pronostics favorables.

Conclusion :

La réalisation de séances bi quotidiennes d'OHB, à une pression de 2.5 ATA, dont la durée totale du traitement est déterminée par l'angiographie à la fluorescéine, semble être un traitement efficace et sûr pour la prise en charge des OACR. La moitié de nos patients a connu une amélioration de l'AV (diminution  $\geq 0.3$  logMAR) à un mois. La mise en place d'un protocole international et standardisé d'OHB semble justifiée pour réaliser des études prospectives et comparatives plus poussées.



Deuxième partie : Thèse au format article

**EFFICACY AND SAFETY OF A STANDARDIZED HYPERBARIC OXYGEN  
THERAPY PROTOCOL FOR RETINAL ARTERY OCCLUSION**

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Word count: 3256

1 figure (colored) and 6 tables.

This work received no grants, no financial support.

No financial or proprietary interests to disclose.

Conflict of interest: none.

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Article submitted for publication in the medical journal RETINA, the journal of retinal and vitreous diseases, on June 14, 2020.

**Running head:** Hyperbaric oxygen therapy in patients with retinal artery occlusion.

**Keywords:** hyperbaric oxygen therapy, central retinal artery occlusion, branch retinal artery occlusion, fluorescein angiography, best-corrected visual acuity.

**Summary statement:** Half of our patients achieved a BCVA improvement ( $\geq 0.3$  logMAR) one month after receiving our standardized hyperbaric oxygen therapy.

## **ABSTRACT**

**Purpose:** To assess the efficacy and safety of a standardized Hyperbaric Oxygen Therapy (HBOT) protocol in patients with Retinal Artery Occlusion (RAO).

**Design:** A retrospective study was conducted in our tertiary care center from July 2016 to September 2019.

**Participants:** Patients experiencing Central RAO and Branch RAO for less than seven days.

**Methods:** Once the diagnosis made, patients were urgently referred to the HBOT department to receive a first 90-minute HBOT session at a pressure of 2.5 ATA. Patients underwent two daily sessions seven days a week, for at least 15 days. If no reperfusion was seen on fluorescein angiography on Day 15, treatment was continued for an additional week with an assessment on Day 21.

**Main outcome measures:** A BCVA improvement was defined as a decrease by 0.3 logMAR at one month.

**Results:** Twenty-eight patients were included during the study period. Fifty-seven percent of patients were treated more than 12 hours after the onset of the first symptoms. The mean BCVA was 1.5 logMAR at the time of referral and improved to 0.9 logMAR after HBOT ( $p=0.001$ ). A multivariate analysis identified a high blood pressure ( $p=0.039$ ) and a low initial BCVA ( $p=0.005$ ) as poor prognostic factors.

**Conclusion:** Performing HBOT sessions twice daily at a pressure of 2.5 ATA appears to be an effective and safe treatment for RAO. Half of our patients achieved a BCVA improvement. Implementing an international standardized HBOT protocol is needed for further prospective, comparative studies.

## INTRODUCTION

Central retinal artery occlusion (CRAO) is a serious and rare vascular disorder involving the retina. The incidence of CRAO is estimated to be approximately 8.5 per 100,000 inhabitants (1). Retinal vascularization relies on the central retinal artery for its inner part whereas the external part relies on the choroidal vessels (2). The occlusion may involve the central retinal artery (CRAO) or one of its branches (Branch Retinal Artery Occlusion: BRAO) (3). The retinal vasculature is terminal without anastomoses between the retinal and choroidal vessels, except when a cilioretinal artery is present as reported in about 25% of patients (4). When CRAO occurs, retinal cells can survive for a few hours due to the oxygen present within the vitreous cavity and the increased anaerobic glycolysis in the visual cells (5). Clinically, CRAO is characterized by a sudden painless loss of vision with a Best-Corrected Visual Acuity (BCVA) usually dramatically reduced to light perception. BRAO is characterized by a sudden visual field defect sometimes associated with a decreased BCVA depending on the location of the occlusion (6). To date, no standard treatment for CRAO has been clearly defined. Several treatments have been used such as pentoxifylline, carbogen inhalation, sublingual isosorbide dinitrate, ocular massage with a three-mirror contact lens, acetazolamide, mannitol, methylprednisolone, tissue plasminogen activator or Neodymium:yttrium-aluminium-garnet (Nd:YAG) laser (7)(8) as well as surgical modalities such as anterior chamber decompression, pars plana vitrectomy with removal of the embolus (9–12).

The Undersea and Hyperbaric Medical Society (UHMS) and the European Committee for Hyperbaric Medicine recommend the use of Hyperbaric Oxygen Therapy (HBOT) for the treatment of CRAO. It consists in delivering a high oxygen pressure through the respiratory tract. HBOT allows increasing both the hydrostatic pressure and the inhaled partial oxygen pressure (13), as well as enhancing red blood cell deformability. HBOT is assumed to act by increasing oxygen supply to hypoxic tissues through the choroidal circulation, thereby preserving the ischemic tissue affected by the occluded retinal artery (2)(14)(15). However, these actions are effective when a high increase in blood oxygen pressure is achieved (16). HBOT includes the inhalation of 100% oxygen at pressures greater than 1 ATA, thus increasing by 20 to 30 the amount of oxygen dissolved in the plasma (14). Under normal physiological conditions, about 60% of the oxygen consumed by the retina is supplied by the choroidal circulation, whereas, under hyperoxic conditions, the choroid can supply 100% of

the oxygen required by the retina (17). It has been suggested that raised oxygen pressures may lead to retinal artery vasoconstriction (18)(19). Interestingly, the choroidal blood flow does not seem to be affected by raised oxygen pressures so that the use of HBOT can significantly increase retinal oxygen supply (15)(17).

HBOT has been previously studied with favorable outcomes when used within 8-24 hours after the occurrence of CRAO (20–26). However, these studies have some limitations, including a small sample size, a lack of ophthalmological examination including fluorescein angiography (FA), a lack of consensus on the HBOT protocol to be used or the main outcome measure.

In addition, a large study has assessed the natural evolution of CRAO without any treatment and has only shown a slight BCVA improvement (3). This finding reinforces the relevance of using HBOT in patients with CRAO.

The aim of our study was to assess the efficacy and safety of a standardized HBOT protocol based on FA in patients experiencing RAO (i.e. CRAO or BRAO).

## **MATERIAL AND METHODS**

### ***Study design and protocol***

A retrospective study was conducted in our French tertiary care center (University Hospital of Nice) from July 2016 to September 2019. The study protocol is summarized in **Figure 1**. Briefly, the diagnosis was made by an ophthalmologist of the University Hospital of Nice. The following examinations were performed: BCVA measurement, slit-lamp examination, dilated fundus examination with color fundus photography, macular Optical Coherence Tomography b-scan (OCT, Heidelberg, Germany), and FA. Once the diagnosis made, the patients were immediately referred to the HBOT department. A clinical examination, a blood test, including blood formulation and inflammatory parameters (sedimentation rate, c-reactive protein) and an electrocardiogram were performed to rule out any contraindication to HBOT. A venous access was obtained when a hypertensive episode occurred during the session. Then, patients received their first HBOT session of 90 minutes at a pressure of 2.5 ATA using a HAUX Comex hyperbaric chamber. At the end of the session, patients underwent a cervical and cerebral CT-scan with contrast injection to rule out any internal carotid dissection or

stenosis and/or associated cerebral stroke. In the absence of any cervical and cerebral abnormalities, patients were discharged and advised to perform a complete cardiovascular examination. Patients received two daily sessions of HBOT (90 min, 2.5 ATA) seven days a week, for at least 15 days. On Day 15, a new ophthalmological examination was performed with BCVA measurement, dilated fundus examination with color fundus photography, and FA. In case of retinal reperfusion, HBOT was discontinued. If no reperfusion was seen, treatment was continued for an additional week with an assessment on Day 21. The maximum treatment duration was 21 days. If retinal occlusion persisted on retinal angiography on Day 21, pan retinal photocoagulation was performed to avoid further ophthalmological complications, including neovascular glaucoma. All patients underwent a final ophthalmological examination at one month for monitoring. In case of significant internal carotid abnormality or associated cerebral stroke diagnosed on the initial CT-scan, patients were referred to the emergency department and were then excluded from the protocol.

#### ***Inclusion and exclusion criteria***

All patients diagnosed with CRAO or BRAO that occurred less than seven days before referral were included. Patients presenting a cilioretinal artery, a concomitant venous occlusion seen on retinal FA, who had received an ophthalmological treatment before referral (anterior chamber puncture, acetazolamide, laser or surgical treatment), who experienced concomitant heart or cerebral stroke, without ophthalmological follow-up or with a HBOT contraindication (sinus and ear disorders, pulmonary emphysema, recent pneumothorax, unbalanced epileptic disease, behavioral disorder, hemodynamic instability) were excluded.

#### ***Data recorded***

Data recorded included: age, sex, type of retinal occlusion (CRAO or BRAO), complete ophthalmological examination findings (BCVA, slit-lamp examination, fundus, OCT and FA), medical history (diabetes status, arterial high blood pressure [HBP], dyslipidemia), medications (antiplatelet or anticoagulant therapy), etiology of CRAO (carotid stenosis or dissection, embolic cardiopathy, other), associated cerebral stroke assessed on the cervical and cerebral CT-scan with contrast injection, occurrence of a hypertensive episode during the HBOT session, time between the occurrence of ocular symptoms and HBOT initiation, number of HBOT sessions and adverse events.

Arterial HBP was defined as a systolic blood pressure  $\geq 140$  mmHg and/or a diastolic blood pressure  $\geq 90$  mmHg, confirmed on two separate measurements or by the intake of

antihypertensive medications. Dyslipidemia was defined according to the French Health Authority as a LDL cholesterol level  $\geq 130$  mg/dL (3.37 mmol/L) or a HDL cholesterol level  $< 40$  mg/dL (1.04 mmol/L) or the use of a lipid-lowering treatment. The diagnosis of embolic heart disease was defined according to the French Society of Cardiology as the presence of atrial fibrillation, atrial flutter, mitral valve disease, patent oval foramen, myocardial infarction, left ventricular aneurysm, bacterial or marastic endocarditis, and myxoma. Carotid stenosis was considered significant when it was symptomatic and greater than 50% or when it was greater than 70% in the absence of symptoms.

### ***Outcome measures***

The main outcome measure was a BCVA improvement defined as a decrease by 0.3 logMAR measured between the referral and Day 30 post-HBOT according to Hadanny et al. (27). The numeric logMAR values for profound low vision categories (counting fingers, hand motion, light perception, and no light perception) were used as proposed by Lange et al. (28).

The secondary outcome measure was a BCVA improvement defined as a decrease by 0.1 logMAR. HBOT side effects were also recorded.

### ***Ethics***

This study was conducted in accordance with the principles outlined in the declaration of Helsinki. Because of the retrospective design of the study, no institutional approval was required. All patients gave their informed consent to participate in the study. Data were anonymized and the study was approved by the French *Commission Nationale Informatique et Liberté* (CNIL number: 2216502).

### ***Statistical analyzes***

Descriptive statistics are presented as numbers and percentages for categorical variables and means  $\pm$  standard deviations (SD) for continuous variables. Analyzes were performed using a Fisher exact test and Student t-tests to compare qualitative and quantitative data, respectively. A multivariate analysis was performed using a multiple logistic regression. SPSS software v.25 (IBM, Chicago, Illinois) was used and a p-value  $< 0.05$  was considered statistically significant.

## RESULTS

Twenty-eight patients were included during the study period. Patient's characteristics are presented in **Table 1**. Patient mean age was 70.1 years (16-89) and 16 (57.1%) patients were males. Thirteen (46.4%) and 7 (25%) patients had a history of arterial HBP and dyslipidemia, respectively. Ten (35.7%) patients were treated with antiplatelets. Fifteen (53.6%) and 13 (46.4%) patients were diagnosed with CRAO and BRAO, respectively. The etiology of retinal occlusion was unknown in 19 (67.8%) patients. For the remaining patients, embolic heart disease was detected in 4 (14.3%) patients and significant carotid stenosis in 5 (17.9%) patients. The CT-scan with contrast injection revealed recent-onset cerebral stroke in 3 (10.7%) patients.

The outcome measures are presented in **Table 2** and **Table 3**. The mean overall BCVA significantly improved from 1.5 logMAR (0-2.3) at the time of referral to 0.9 logMAR (0-2.3) at one month ( $p=0.001$ ). In the CRAO subgroup, the mean BCVA significantly improved from 1.9 logMAR (0.1-2.6) at the time of referral to 1.4 logMAR (0-2.3) at one month ( $p=0.013$ ). Revascularization assessed on FA occurred in 11 (39.2%) patients (14.2% on Day 14 and another 25% on Day 21). Data were missing for the remaining 17 patients. The time between the occurrence of the first ocular symptoms and HBOT initiation was  $\leq 12$  hours in 12 (42.9%) patients. Twenty-three (82.1%) patients underwent their first session within one hour of their arrival in the HBOT department. A mean number of 34.4 HBOT sessions were performed per patient, twice daily in 20 (71.4%) patients, and once daily in 8 (28.6%) patients. Seven (25%) patients experienced a hypertensive episode during the HBOT session, and 6 (21.4%) experienced a barotrauma for which no HBOT discontinuation was required.

In the univariate analysis, arterial HBP ( $p= 0.008$ ), dyslipidemia ( $p=0.038$ ), the use of antiplatelets ( $p=0.033$ ) and a low baseline BCVA ( $p=0.001$ ) were identified as poor prognostic factors for BCVA improvement. Experiencing a barotrauma during a HBOT session was associated with a better prognosis ( $p=0.036$ ). In the multivariate analysis, only arterial HBP ( $p=0.039$ ) and a low baseline BCVA ( $p=0.005$ ) were associated with a poor prognosis (**Table 4**).

In the subgroup of CRAO patients ( $n=15$ ), diabetes ( $p=0.042$ ) and an embolic heart disease ( $p=0.049$ ) were associated with a poor prognosis in the univariate analysis (**Table 5**) whereas benefiting from a rapid initial management ( $p=0.042$ ) and receiving HBOT sessions twice



daily ( $p=0.032$ ) were considered as favorable prognostic factors. The multivariate analysis failed to identify any prognostic factor.

## DISCUSSION

In this retrospective study, we focused on the improvement in BCVA in patients with CRAO and BRAO treated with HBOT in our tertiary care center. In our study, 14 (50%) patients achieved a BCVA improvement  $\geq 0.3$  logMAR. No major side effects were reported during the HBOT sessions.

As shown in **Table 6**, comparing our results with the current literature appears challenging because of a lack of consensus regarding the main outcome measures, the recommended HBOT protocol (number of sessions, pressure applied) and the ancillary procedures performed (ocular massage, acetazolamide, anterior chamber paracentesis...) (29). In addition, the ophthalmological examination is often limited to BCVA measurement and fundus examination (24).

Our results are in accordance with most of the previous studies that have reported a BCVA improvement following HBOT in RAO patients (14)(21)(26)(27)(30) (**Table 6**). In their study, Beiran et al. have observed a BCVA improvement in 82.9% of patients, a value that is higher than our results (26). This could be explained by a better baseline BCVA in their study (1 logMAR) compared to our patients (1.5 logMAR) (26). This could also be explained by the fact that their main outcome measure was a BCVA improvement  $\geq 3$  lines in the Snellen chart whereas we used the logMAR visual scale in our study. In addition, they have only included patients whose symptoms appeared less than eight hours before referral. Weinberger et al. have found a BCVA improvement in 90.5% of their patients (21). However, these results should be interpreted with caution because the BCVA was not evaluated by an ophthalmologist but by the patients themselves (subjective evaluation).

CRAO etiologies have been investigated in previous studies. In our study, we identified an embolic heart disease and significant carotid stenosis in 14.3% and 17.9% of patients, respectively. Hayreh et al. have identified an arterial origin in 5% of patients and Elder et al. an embolic heart disease in 9.7% of patients (3)(30).

In our study, both CRAO and BRAO patients were included. CRAO was more common than BRAO (53.6% versus 46.4%). This finding was in line with the results reported

by Beiran et al., who have found an over-presentation of CRAO patients (82.9%) compared to BRAO patients (17.1%) (26).

Our study is the first to investigate the rate of cerebral stroke in patients treated with HBOT for RAO. We identified 10.7% of patients experiencing cerebral stroke. Hadanny et al. have only recorded a past medical history of cerebral stroke in their patients (27). Some studies have shown that RAO was associated with increased rates of cerebral stroke and mortality within five years of the vascular event (31–33). In addition, it should be noted that the beneficial effects of HBOT on stroke have been suggested in several experimental studies (34). However, the efficacy of HBOT in patients experiencing cerebral stroke is not well established due to the lack of randomized clinical trials (35).

In our study, a prompt management with HBOT was identified as a favorable prognostic factor in the univariate analysis ( $p=0.042$ ). This finding is consistent with the study by Elder et al. (30). We performed two daily HBOT sessions as many other authors (14)(21)(24)(26). However, it should be noted that Beiran et al. and Cope et al. have performed two daily sessions only during the first three days, and have continued with only one session per day during the rest of the treatment (26)(14). This is probably due to the fact that no study has shown the superiority of two daily sessions over a single session. Moreover, it can be logistically complicated for patients to undergo HBOT sessions twice a day. As previously stressed by Beiran et al., we tried to reduce the time between two consecutive HBOT sessions to less than 24 hours (26). As reported by Cope et al., a pressure of 2.5 ATA was applied to all patients (14).

Our patients received a mean number of 34.4 HBOT sessions. As shown in **Table 6**, this value is higher than in other studies (14)(21)(24)(26)(27)(30). This could be explained by the fact that we performed two daily sessions until revascularization of the retinal artery assessed on FA (on day 15 or day 21). To date, no clear international consensus on HBOT for the treatment of RAO has been proposed.

We identified HBP ( $p=0.008$ ), dyslipidemia ( $p=0.038$ ), diabetes mellitus ( $p=0.042$ ), embolic heart disease ( $p=0.049$ ) and the use of antiplatelets ( $p=0.033$ ) as poor prognostic factor in RAO. This could be explained by the fact that hypertensive and diabetic patients have a weaker arterio-venous network, partially sclerosed or overloaded with atheroma (36). The role of antiplatelets is debated. In our study, being treated with acetyl salicylic acid was associated with a poorer prognosis whereas in the study conducted by Menzel et al., it has been identified as a good prognostic factor (24). It could be assumed that antiplatelets could

reduce the size of the embolus by reducing platelet aggregation. On the other hand, patients treated with antiplatelets are at higher vascular risk with an impaired vascular network.

We found that a low baseline BCVA was associated with a poorer visual prognosis. This is in line with Hadanny et al. who have found that the presence of a cherry red spot in the fundus upon presentation was a poor factor for referral (27). A cherry red spot usually appears a few hours after the occurrence of RAO and leads to a late referral.

In our study, 6 (21.4%) patients experienced a barotrauma for which no HBOT discontinuation was required. One (3.2%) and 3 (2.3%) patients in the studies conducted by Elder et al. and by Hadanny et al. have respectively experienced a barotrauma (30)(27). The relationship between the occurrence of a barotrauma and a better visual recovery could not be clearly explained. An early management and receiving two daily sessions were also associated with a favorable prognosis. Seven (25%) patients experienced a hypertensive episode during the HBOT session. Apart from the reported cases of barotrauma, 5 patients in Hadanny's study have experienced HBOT-related adverse events: two (1.5%) patients had otalgia without barotrauma signs and one of them (0.7%) underwent myringotomy in order to continue the HBOT sessions; one (0.7%) patient experienced mild epistaxis unrelated to the barotrauma that resolved spontaneously; one (0.7%) patient experienced dyspnea during one of the sessions and recovered a few minutes after the session (27).

In our study, the protocol was terminated early in 5 patients (three with recent stroke and two claustrophobic patients). These patients received 3, 5, 14, 16, and 21 HBOT sessions, respectively. These early discontinuations could have biased our results even if it could be assumed that this potential bias would rather be in disfavor of the efficacy of HBOT. Regarding the events leading to early treatment discontinuation, Elder et al. have reported respiratory infection and an episode of claustrophobia (30).

Our study has some limitations. First, it is a retrospective study with a small sample size. However, CRAO and BRAO are rare disorders and this could explain the small number of patients included. Due to its retrospective design, some examinations such as FA could sometimes not be performed. Second, our study was not comparative. However, no standard of care for treating CRAO has been proposed in the literature (3). Hayreh et al. have studied the natural evolution of CRAO patients and shown that only a minor visual improvement (1.7 to 1.5 logMar) occurred without any treatment (3). Compared to our study, Hayreh et al. have shown an improvement in visual acuity in 22% of eyes with non-arteritic CRAO, while the visual acuity improved in 50% of our patients, with a mean regression by 0.6 logMAR at the end of the study (1.5 to 0.9 logMAR).

The strength of this study is the cooperation between the ophthalmological and hyperbaric departments. All patients underwent a complete ophthalmological examination before referral to the HBOT department. The protocol also included the monitoring of cardiovascular disorders as well as a close multidisciplinary follow-up when possible. HBOT discontinuation was based on retinal FA performed by the ophthalmology department and allowed a better monitoring of the retinal revascularization. In case of arterial reperfusion on Day 14, HBOT discontinuation was decided. This HBOT protocol was more in line with the pathophysiology of RAO and we recommend the use of our protocol in such cases. Finally, our primary outcome measure was based on a previous robust study (27) and was assessed by an ophthalmologist and not subjectively by the patients themselves (3)(21).

## **CONCLUSION**

HBOT, administered twice a day at a pressure of 2.5 ATA and monitored by FA, appears to be an effective and safe treatment for RAO (CRAO and BRAO). Half of our patients achieved a BCVA improvement ( $\geq 0.3$  logMAR) at one month. Implementing an international standardized HBOT protocol is needed for conducting further prospective, comparative studies. HBOT duration should be based on FA monitoring.

## **ACKNOWLEDGEMENTS**

To all the secretaries of the Hyperbaric Oxygen department and Ophthalmology department for their help to organize all the appointments.

## **FUNDINGS**

None.

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## **FIGURE LEGENDS**

**Figure 1a:** OCT of a physiological vascularization of the retina

**Figure 1b:** OCT of a central retinal artery occlusion

**Figure 1c:** Effect of HBOT on the vascularization of the central retinal artery

**Figure 2:** Standardized HBOT protocol used in the present study

## **TABLE LEGENDS**

**Table 1:** Patient's characteristics

**Table 2:** Primary outcome result

**Table 3:** Secondary outcome result

**Table 4:** Prognostic factors associated with BCVA improvement (BCVA decrease by 0.3 logMAR) in all patients (CRAO + BRAO)

**Table 5:** Prognostic factors associated with BCVA improvement (BCVA decrease by 0.3 logMAR) in CRAO patients only

**Table 6:** Literature review of HBOT in RAO



SUPPLEMENTARY MATERIALS

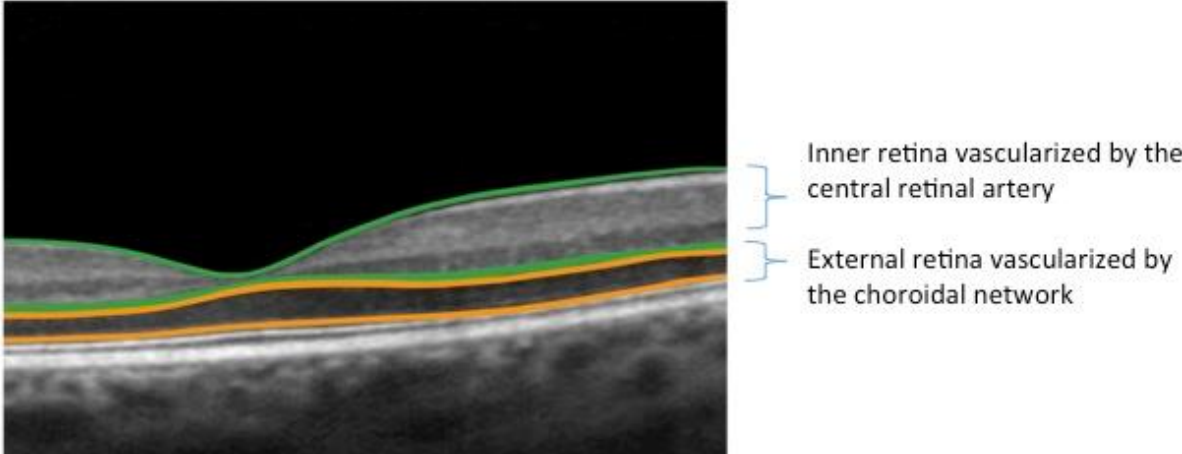


Figure 1a

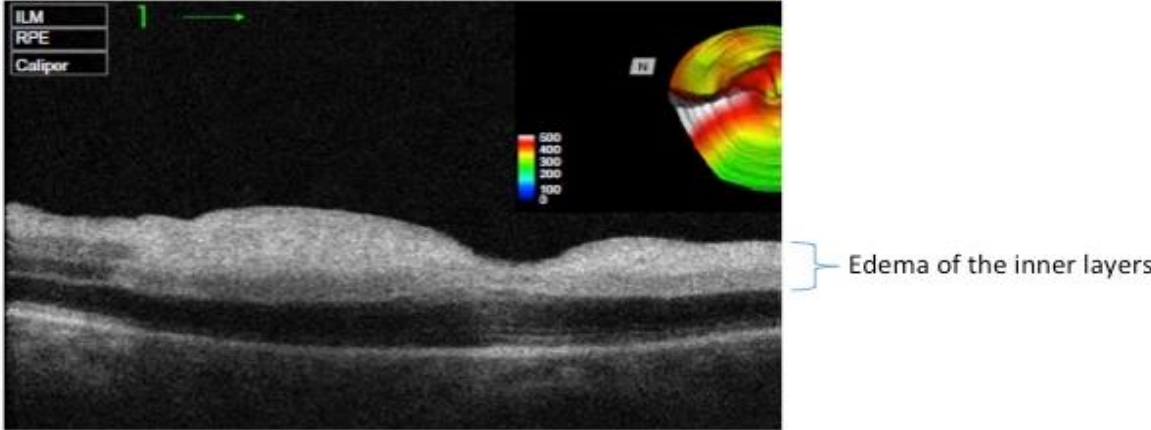


Figure 1b

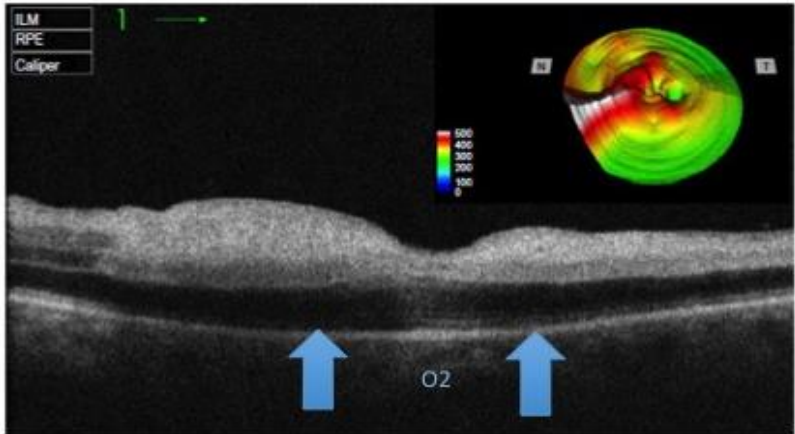
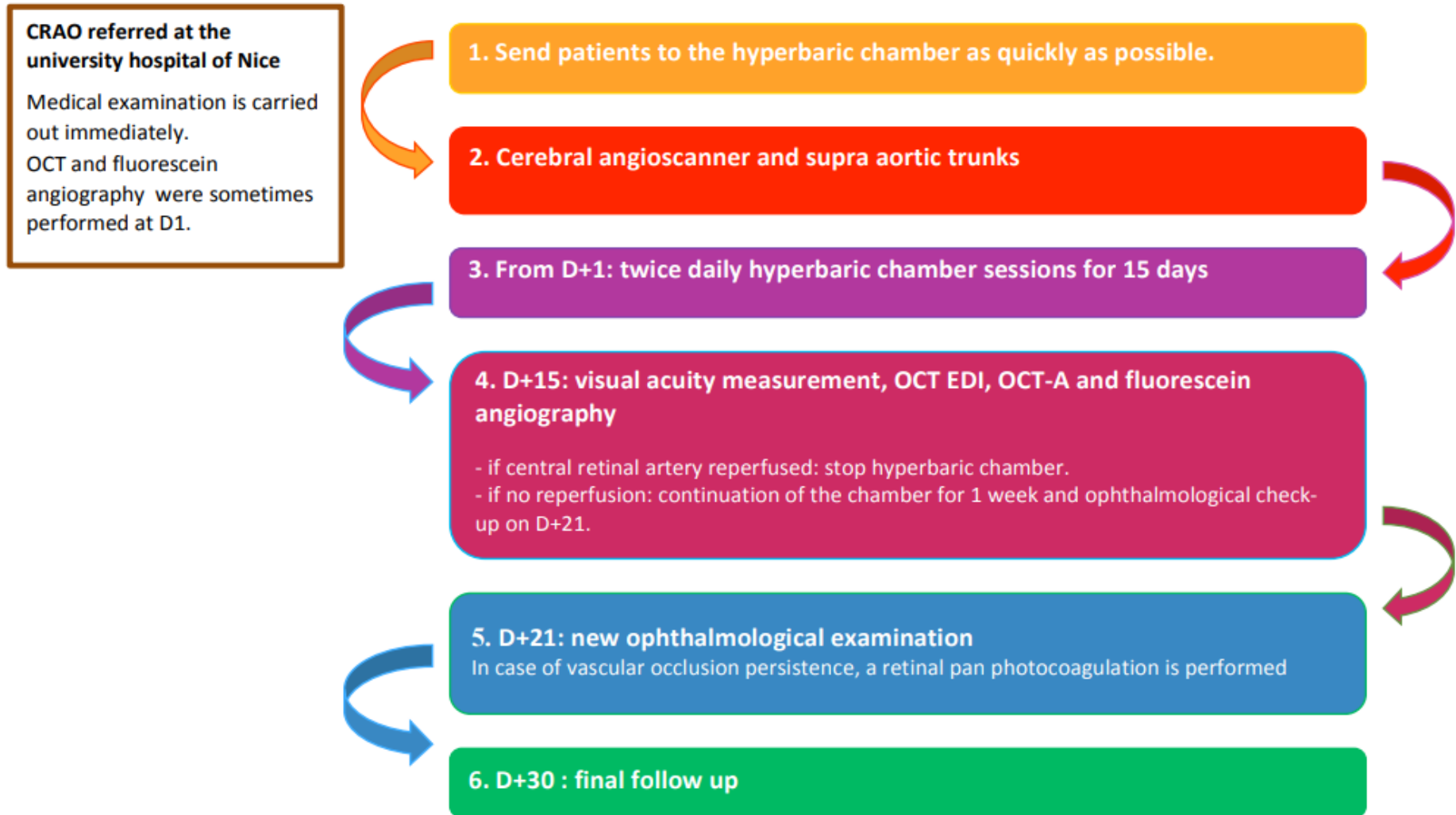


Figure 1c

Figure 2: HBOT protocol



<b>Patients characteristics</b>	<b>Number (%)</b>	<b>Mean (Range)</b>
<b>Male</b>	16 (57.1)	
<b>Woman</b>	12 (42.9)	
<b>Age (years)</b>		70.1 (16-89)
<b>Smocking status:</b>		
<b>Yes</b>	4 (14.3)	
<b>No</b>	8 (28.6)	
<b>NA</b>	16 (57.1)	
<b>High blood pressure:</b>		
<b>Yes</b>	13 (46.4)	
<b>No</b>	15 (53.6)	
<b>Dyslipidemia:</b>		
<b>Yes</b>	7 (25)	
<b>No</b>	21 (75)	
<b>Diabetes:</b>		
<b>Yes</b>	1 (3.6)	
<b>No</b>	27 (96.4)	
<b>Anticoagulant therapy:</b>		
<b>Yes</b>	2 (7.1)	
<b>No</b>	26 (92.9)	
<b>Antiplatelet drug:</b>		
<b>Yes</b>	10 (35.7)	
<b>No</b>	17 (60.7)	
<b>NA</b>	1 (3.6)	
<b>Type of retinal occlusion:</b>		
<b>CRAO</b>	15 (53.6)	
<b>BRAO</b>	13 (46.4)	
<b>Aetiology of RAO:</b>		
<b>Embolic heart disease</b>	4 (14.3)	
<b>Carotid stenosis</b>	5 (17.9)	
<b>Not determined</b>	19 (67.8)	
<b>Stroke revealed on CT scan</b>		
<b>Yes</b>	3 (10.7)	
<b>No</b>	24 (85.7)	
<b>NA</b>	1 (3.6)	

**Table 1: Patient's characteristics**

	<b>Number of patients</b>	<b>Baseline BCVA (range)</b>	<b>BCVA at one month (range)</b>	<b>Number of patients (%) with BCVA improvement <math>\geq</math> 0.3 logMar</b>	<b>P value</b>
<b>All patients (CRAO + BRAO)</b>	28	1.5 (0-2.3)	0.9 (0-2.3)	14 (50%)	0.001
<b>CRAO patients only</b>	15	1.9 (0.1-2.6)	1.4 (0-2.3)	10 (66.7%)	0.013

**Table 2: Main outcome results.**

	<b>Number (%)</b>
<b>Secondary outcome measure: BCVA improvement <math>\geq</math> 0.1 logMAR</b>	16 (57.1)
<b>Ocular angiography revascularization:</b>	
Day 14	4 (14.2)
Day 21	7 (25)
No revascularization	2 (7.1)
NA	15 (53.6)
<b>Treatment initiated (Anticoagulant therapy or Antiplatelet drug)</b>	
Yes	8 (28.6)
No	4 (14.3)
NA	16 (57.1)
<b>Time elapsed between ocular symptoms and first HBOT</b>	
< 12h	12 (42.9)
> 12h	16 (57.1)
<b>Time elapsed from arrival at the hyperbaric department to the first hyperbaric session</b>	
< 1h	23 (82.1)
> 1h	5 (17.9)
<b>HBOT induced Barotrauma</b>	
Yes	6 (21.4)
No	22 (78.6)
<b>Hypertensive crisis during hyperbaric session:</b>	
Yes	7 (25)
No	21 (75)
<b>Hyperbaric session:</b>	
Once daily	8 (28.6)
Twice daily	20 (71.4)
<b>Time between two hyperbaric sessions:</b>	
< 24h	24 (85.7)
> 24h	4 (14.3)

**Table 3: Secondary outcomes results (CRAO + BRAO patients).**

Visual acuity decrease $\geq 0.3$ logMAR	Univariate analysis <i>p value</i>	Multivariate analysis <i>p value</i>
<b>CRAO</b>	0.123	-
<b>BRAO</b>	0.123	-
<b>Smoking status</b>	0.188	-
<b>High Blood pressure</b>	<b>0.008</b>	<b>0.039</b>
<b>Dyslipidemia</b>	<b>0.038</b>	0.167
<b>Diabetes</b>	0.076	-
<b>Anticoagulant medication</b>	0.143	-
<b>Antiplatelet medication</b>	<b>0.033</b>	0.867
<b>Embolic heart disease</b>	0.183	-
<b>High blood pressure at arrival in the hyperbaric department</b>	0.169	-
<b>Hypertensive crisis during hyperbaric session</b>	0.126	-
<b>Carotid stenosis</b>	0.079	-
<b>Recent stroke revealed on CT scan</b>	0.130	-
<b>Etiology (stenosis, embolus)</b>	0.204	-
<b>First hyperbaric session &lt;12h after blindness</b>	0.083	-
<b>HBOT initiated in the first hour after arrival at the hyperbaric oxygen department</b>	0.135	-
<b>Barotrauma</b>	<b>0.036</b>	0.993
<b>Twice daily sessions</b>	0.157	-
<b>Time &gt; 24h between two sessions</b>	0.183	-
<b>Treatment initiated (antiplatelet drug or anticoagulant medication)</b>	0.101	-
<b>Number of hyperbaric sessions</b>	0.613	-
<b>BCVA at referral</b>	<b>0.001</b>	<b>0.005</b>

**Table 4: Prognostic factors associated with the main outcome measurement (BCVA decrease  $\geq 0.3$  logMAR) for all patients (CRAO + BRAO)**

Visual acuity decreased of 0.3 logMAR	Univariate analysis <i>p value</i>	Multivariate analysis <i>p value</i>
Smoking status	0.359	-
High Blood pressure	0.066	-
Dyslipidemia	0.066	-
Diabetes	<b>0.042</b>	0.191
Anticoagulant medication	0.062	-
Antiplatelet medication	0.136	-
Embolic heart disease	<b>0.049</b>	0.438
High blood pressure at arrival on the hyperbaric department	0.143	-
Hypertensive crisis during hyperbaric session	0.138	-
Carotid stenosis	0.205	-
Recent stroke revealed on CT scan	0.264	-
Etiology (stenosis, embolus)	0.146	-
First hyperbaric session <12h after blindness	0.143	-
HBOT initiated in the first hour after arrival at the hyperbaric oxygen department	<b>0.042</b>	0.443
Barotrauma	0.113	-
Twice daily sessions	<b>0.032</b>	0.844
Time > 24h between two sessions	0.155	-
Treatment initiated	0.324	-
Number of hyperbaric sessions	0.587	-
BCVA at referral	0.105	-

**Table 5: Prognostic factors associated with the main outcome measurement (BCVA decrease  $\geq 0.3$  logMAR) for CRAO patients only.**

<b>Authors, year</b>	<b>Beiran et al, 2001</b>	<b>Weinberger et al, 2002</b>	<b>Cope et al, 2011</b>	<b>Menzel-Severing et al, 2012</b>	<b>Hadanny et al, 2016</b>	<b>Elder et al, 2017</b>	<b>Ilbasmis et al, 2018</b>	<b>Di Vincenzo et al, 2020</b>
<b>Study design</b>	Retrospective Comparative	Prospective Non comparative	Retrospective Non comparative	Retrospective Non comparative	Retrospective	Retrospective Non comparative	Prospective study	Retrospective Non comparative
<b>No. Of patients</b>	72 (35 HBOT vs 37 no treatment)	21	11	80 (51 HBOT + hemodilution vs 29 hemodilution only)	128	31	16	28
<b>Mean age (years)</b>	69.5 (HBOT group)	NA	61	69 (HBOT group)	66.4	70	49	70.1
<b>Inclusion criteria</b>	RAO <8h	CRAO <12h	CRAO	RAO <12h VA <20/200	CRAO <20h VA < 0.5 logmar	Non arteritic ARAO	RAO	RAO (CRAO + BRAO) <7 days
<b>Etiology of CRAO</b>	NA	NA	NA	Cardiovascular disorder Arteritic CRAO excluded	Unknown (66,4%) Carotid atherosclerosis (18%) Emboli (11%)	Carotid stenosis (9.7%)	NA	Unknown (67.8%) carotid stenosis (17.9%) embolic heart disease (14.3%)



Authors, year	Beiran et al, 2001	Weinberger et al, 2002	Cope et al, 2011	Menzel-Severing et al, 2012	Hadanny et al, 2016	Elder et al, 2017	Ilbasmis et al, 2018	Di Vincenzo et al, 2020
<b>Type of RAO</b>	CRAO (82.9%) BRAO (17.1%)	NA	NA	CRAO	Only non arteritic CRAO	CRAO (96.8%) BRAO (3.2%)	NA	CRAO (53.6%) BRAO (46.4%)
<b>Stroke associated with CRAO</b>	NA	NA	NA	NA	24 patients in previous medical conditions	NA	NA	3 (10.7%)
<b>Therapy</b>	HBOT vs nothing	HBOT + hemodilution	HBOT	HBOT + hemodilution vs hemodilution only	ocular massage, anterior chamber paracentesis, oral aspirin, oral acetazolamide, or topical beta-blocker were applied prior to HBOT	HBOT + oral acetazolamide HBOT + ocular massage HBOT + anterior ocular chamber paracentesis HBOT + dipryidamole HBOT + aspirin HBOT + heparin HBOT + clopidogrel	HBOT	HBOT

<b>Authors, year</b>	<b>Beiran et al, 2001</b>	<b>Weinberger et al, 2002</b>	<b>Cope et al, 2011</b>	<b>Menzel-Severing et al, 2012</b>	<b>Hadanny et al, 2016</b>	<b>Elder et al, 2017</b>	<b>Ilbasimis et al, 2018</b>	<b>Di Vincenzo et al, 2020</b>
<b>BCVA at referral logMAR Mean (range)</b>	1	(1.1-2.3)	2.2 (0.4-2.6)	1.8 (SD 0.3)	2.1	2 (0.2-2.3)	NA	1.5 (0-2.3)
<b>Visual acuity after HBOT logMAR Mean (range)</b>	0.5	NA	1.4 (0.4-2.3)	1.5	1.6	1.6 (0-2.6)	NA	0.9 (0-2.3)
<b>Primary endpoint</b>	≥ 3 lines (Snellen scale)	Subjective visual improvement	> 2 lines (Snellen scale)	≥ 3 lines (Snellen scale)	Decrease of 0.3 logMAR	Visual improvement (Snellen scale)	Subjective visual improvement	Decrease of 0.3 logMAR
<b>Visual improvement (%) according to the primary endpoint</b>	82.9 vs 29.7 (p<0.00001)	90.5	74	38.8 on discharge 35.7 at three months	67.2	74	81.2	75
<b>Factors associated with good prognosis</b>	High blood pressure	NA	No	Patients under Acetyl salycilic acid	NA	Age Delay to 1st HBOT<10h	NA	Barotrauma, Twice daily session, Delay to first HBOT

<b>Authors, year</b>	<b>Beiran et al, 2001</b>	<b>Weinberger et al, 2002</b>	<b>Cope et al, 2011</b>	<b>Menzel-Severing et al, 2012</b>	<b>Hadanny et al, 2016</b>	<b>Elder et al, 2017</b>	<b>Ilbasmis et al, 2018</b>	<b>Di Vincenzo et al, 2020</b>
<b>Factors associated with poor prognosis</b>	NA	NA	No	NA	Cherry red spot at presentation	No	NA	High blood pressure Diabetes Embolic heart disease Acetyl salycilic acid
<b>Mean delay to HBOT (hours)</b>	NA	4-12h	35	< 12 hours	7.8 +/- 3.8 h	3-25.5h	28	<12h (42.9%) >12h (57.1%)
<b>Mean HBOT number (range)</b>	NA	NA	7 (5-21)	5	4	4 (1-7)	8 (1-20)	34.4
<b>Number of daily HBOT session</b>	Twice daily the first three days then once daily, stop if no improvement at three consecutive treatment	2	Twice daily for the first five treatments then daily	1 to 2	Three times the first three days then once daily	NA	Three times in first day, twice daily on days two and three and once daily for at least another four days.	2

<b>Authors, year</b>	<b>Beiran et al, 2001</b>	<b>Weinberger et al, 2002</b>	<b>Cope et al, 2011</b>	<b>Menzel-Severing et al, 2012</b>	<b>Hadanny et al, 2016</b>	<b>Elder et al, 2017</b>	<b>Ilbasimis et al, 2018</b>	<b>Di Vincenzo et al, 2020</b>
<b>Time between two HBOT sessions</b>	12 hours the first three days then 24 hours	NA	NA	5 times within 48 hours, with 3 treatments within the first 24 hours.	NA	NA	NA	<24h (875.7% of patients)
<b>Pressure (ATA)</b>	2.8	NA	2.5	2.4	2-2.4	1st session: 2 or 2,4 during 90' or 2,8 during 60' and 2,4 for subsequent session	2.4	2.5
<b>Barotrauma (%)</b>	NA	NA	No	0	3 (2.3)	1 (3.2)	NA	6 (21.4)

**Table 6: Literature comparison**

NA : not available

SD: standard deviation

ARAO: acute retinal artery occlusion

VA: visual acuity

### Troisième partie : Serment d'Hippocrate

Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque.

*« Guérir parfois, soulager souvent, écouter toujours »,*

Louis Pasteur