Does hyperbaric oxygen (HBO) delivery rescue retinal photoreceptors in retinitis pigmentosa?

ENZO MARIA VINGOLO¹, PAOLO PELAIA², RENATO FORTE¹, MONICA ROCCO⁵, CRISTIANO GIUSTI¹ & EDUARDO RISPOLI¹
¹Chair of Ophthalmology, Department of Ocular Electrophysiology, Center for Inherited Degenerative Retinal Disorders, University of Rome ‘La Sapienza’
²Institute of Anaesthesiology and Reanimation, University of Rome ‘La Sapienza’

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Abstract. As previously reported in the literature, hyperbaric oxygen delivery seems to modify the natural course of retinitis pigmentosa. In order to evaluate these first encouraging data, 48 affected subjects were separately studied in two subgroups (cases and controls). All patients underwent yearly an ophthalmological examination completed by a maximum amplitude electroretinogram, conducted according to our ‘differential derivation’ system, a new recording technique specifically designed to enhance the signal-to-noise ratio. Oxygen delivery was provided regularly for 90 min daily (2.2 Absolute Atmosphere) in three cycles according to a standard protocol. In the cases, electroretinographic mean values were as follows: at TO (baseline) 4.68 ± 3.81 μV; after one year (T1) 8.45 ± 5.71 μV; at two years (T2) 10.7 ± 7.6 μV; at the end of the study (T3) 14.4 ± 11.7 μV. In the controls, electroretinographic mean values were as follows: at TO 4.92 ± 3.05 μV; at T1 5.04 ± 3.07 μV; at T2 3.46 ± 2.77 μV; at T3 2.97 ± 3.61 μV. Amplitudes showed a remarkable (p<0.001) increase in the cases, while a slightly significant (p<0.02) decrease was evident at the end of the study in the controls. In our opinion, retinal oxygen availability may be critical in retinal degeneration and hyperbaric oxygen delivery, inducing hyperoxia, seems to be able to bring about the rescue of the retinal photoreceptors helping them in their metabolic requirements. Unfortunately, our study demonstrates an increase in electroretinographic responses only, which may not necessarily also mean an evident change in visual acuity.

Key words: electroretinogram, electrophysiology, hyperbaric oxygen delivery, retina, retinitis pigmentosa

Abbreviations: HBO—Hyperbaric Oxygen; RP—Retinitis Pigmentosa

Introduction

Retinitis pigmentosa (RP) is an inherited degenerative retinal disorder characterized by electroretinographic (ERG) response alterations of various degrees associated with progressive clinical features [1–5] most of which are not suit-
able for treatment: therefore, no therapy, able to modify the natural course of the disease, is generally available for most patients [2].

However, many authors suggest that normal retinal photoreceptors have an increased oxidative metabolism and are strictly conditioned by oxygen partial pressure in peripheral tissues [6–8]. Therefore, several authors propose different treatments involving photoreceptor metabolism (dopamine; dark glasses; antioxidants; vitamins A and E) [9, 10].

Except in our previous preliminary studies [11–13], hyperbaric oxygen delivery (HBO) has never been tested in randomized trials, even though, in theory, it might be of great importance in modifying RP’s natural course [14]. It was therefore the purpose of this investigation to evaluate much more precisely the role of oxygen delivery in influencing photoreceptorial death and rescue.

Materials and methods

Two groups of 24 RP subjects were randomly selected from our patient population in order to avoid interference by selection bias and, thereafter, studied during a three-year period; at the beginning of the study the mean ages of both groups were as follows: group A (cases; 14 males and 10 females) = 33.6 ± 11.7 years (range, 20–58 years); group B (controls; 16 males and 8 females) = 32.8 ± 12.4 years (range, 18–55 years).

The diagnosis of RP was based on the clinical, genetic and instrumental criteria established by Marmor et al. [4]. Only patients whose inheritance pattern was clearly identified were selected for this study: autosomal dominant, autosomal recessive or X-linked forms were considered. In all patients, ERG and clinical data were consistent with a typical rod-cone degenerative disorder (inclusion criteria). Patients who showed a definite cone-rod pattern or were affected by RP syndromic forms (i.e., Usher or Laurence-Moon-Bardet-Biedl) were not included in this study (exclusion criteria). Moreover, we excluded also patients with visual acuity lower than 0.4 (20/50), or unrecordable, flat ERGs.

Before starting the therapeutic protocol, all necessary ethical approvals were obtained by the University committee; the study itself was conducted in compliance with the Declaration of Helsinki. All patients were fully informed about HBO’s risks and benefits and, thereafter, undersigned their consent. The chance to stop therapy was guaranteed to any subject at any time.

Patients of group A were treated with HBO therapy as follows: 90 min O₂ daily (2.2 Absolute Atmosphere [ATA] or 12 m undersen), five times a week for the first month; one week a month for the following 11 months; one week
every three months for the following two years. Patients of group B were studied as a control group during the same interval.

This schedule was assessed some years ago in a preclinical trial in which the better treatment interval, in order to avoid both HBO’s toxic effects and decrease in retinal activity due to long-term suspension of therapy, was evaluated [11].

All patients underwent yearly (T0, T1, T2, T3) a careful ophthalmological examination and maximum amplitude electroretinogram (ERG). Maximal ERG responses [15] were recorded according to our low-noise methods, elsewhere described in greater detail [16, 17]. In brief, 100 iterations, elicited with a 10-μs standard flash from a dark-adapted eye (after full pupillary dilation and 20 min dark adaptation) with a full-field 20-lux/s 0.5 Hz flash stimulation, were recorded and off-line averaged in order to evaluate the retinal response. Henkes-type corneal electrodes, connected to a mechanical, continuously controlled suction pump, were employed to record the tracings. In case of extreme reduction of the signal, a ‘differential derivation’ system was used (electrode on the patched fellow eye used as a reference) resulting in a substantial increase in the signal-to-noise ratio [16, 17].

Amplitude of the signal and a-wave and b-wave peak times were determined according to standard criteria [15]. ERG b-wave amplitudes were expressed and statistically analyzed both as raw data (in microvolts [μV]) and after conversion to log units, while peak times were determined in milliseconds.

The data were statistically analyzed by means of Student’s ‘T’ test and χ² test (Apple Macintosh, StatView II program). Statistical significance was expressed in terms of p values at 0.05 or less. Moreover, we considered as unchanged ERG those in which amplitude did not increase or worsen relative to the basal value ± standard error (SE) of the sample.

This study was not conducted in a double mask system. In fact, for a three-year period, hyperbaric therapy needs active collaboration in order to reach adequate O₂ levels and air itself contains a sufficient quantity of oxygen that might bias the study.

Results

In detail, ERG b-wave mean amplitudes resulted in the cases as follows: at T0 4.68 ± 3.81 μV; after one year (T1) 8.46 ± 5.71 μV; at two years (T2) 10.7 ± 7.6 μV; at the end of the study (T3) 14.4 ± 11.7 μV. In the controls, b-wave mean values were as follows: at T0 4.92 ± 3.05 μV; at T1 of 5.04 ± 3.07 μV; at T2 3.46 ± 2.77 μV; at T3 2.97 ± 3.61 μV. ERG amplitudes during treatment showed a remarkable (p<0.001) increase in the cases, while
a slightly significant (p<0.02) worsening was observed at the end of the study
in the controls (Figure 1).

After a three-year follow up, HBO therapy resulted in an improvement
in 11% of patients while in 89% ERG data remained unchanged. Opposite
results were found in the controls, where 62% showed a worsening of ERG
b-wave amplitudes while only 38% of subjects showed unchanged electroretin-
ographic responses. All these reported differences between group A and
group B resulted statistically significant (χ² 41.056; p<0.001) (Figure 2).
Conversion from μV to log units did not affect these findings; other variables,
such as a-wave and b-wave peak times, resulted insignificant in our study.

Discussion

Photoreceptor damage has several pathogenetic hypotheses: probably, the
main involvement is in the phototransduction process. In fact, it implies dif-
ferent steps with several proteins that in case of quantitative or qualitave
alteration may cause premature cellular death.

The different forms of retinopathies (autosomal dominant and recessive
RP and also the most frequent X-linked) are associated with point muta-
tions, intragenic microdeletions and several others molecular defects within a range above 20 different RP loci. Genetic analysis has defined more than 10 chromosomal regions carrying RP genes and several of them, underlying autosomally inherited forms, have been identified: e.g., gene which code for rhodopsin, \( \alpha \)- and \( \beta \)-subunits of the rod-specific cGMP-phosphodiesterase, peripherin, and rod outer membrane protein (ROM1). All these mutations affect proteins which are involved in the phototransduction process or in the photoreceptorial cytoarchitecture.

Subjects affected by typical RP show a heterogeneous group of disorders (night blindness, progressive visual field constriction and ‘pigmented’ fundus abnormalities) due to the gradual photoreceptorial degeneration, which progresses from the periphery to the central region of the retina [1].

Variability of clinical expression [2] exists among patients with these mutations suggesting that other factors might influence the natural course of this pathology.

Retinal photoreceptors are very sensitive to the oxygen supply as demonstrated both by Stone's studies in vivo on rodents [18] and our previous observations in patients affected by chronic lung disease [19].

Moreover, our preliminary studies seem to indicate that retinal oxygen availability may be a critical point in the development of retinal degeneration [11–13]. In fact, according to Stone [18], this condition of transient
hyperoxia may rescue retinal photoreceptors, probably by helping them to complete their metabolic requirements, and may result in increased maximal ERG responses that last for several months. The significant improvement in ERG b-wave amplitude, obtained in the present study, seems to confirm this hypothesis.

Moreover, a clear indication that a metabolic supply might positively influence the RP natural course has been reported by Berson who demonstrated increased ERG responses after treatment with vitamin A [12]. In the same study, ERG was recognized as a very useful method for evaluation of both retinal function and RP progression.

One last question: why is HBO delivery more effective than normal breathing? In normal breathing hemoglobin O₂ saturation is very high (about 97%); on the contrary, in hyperbaric conditions, the amount of oxygen dissolved in the plasma increases considerably, depending on partial pressure at lung levels (about 60% at -15 m of depth). Thus, HBO activity may be applied in different sites in which a higher metabolic supply is needed especially if a genetically inherited disorder of the phototransduction process is present.

In summary, our investigation may not be considered conclusive because of the small number of patients involved and the short follow-up. However, in this pilot study HBO delivery determined a remarkable (p<0.001) increase of ERG b-wave mean amplitudes, while a slightly significant (p<0.02) decrease was evident at the end of the study in the controls. In our opinion, retinal oxygen availability may be critical in retinal degeneration and HBO delivery, inducing hyperoxia, seems to be able to bring about the rescue of retinal photoreceptors helping them in their metabolic requirements. Unfortunately our study demonstrates an increase in ERG responses only, which may not necessarily also imply an evident change in visual acuity.

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References


Address for correspondence: C. Giusti, Via Cassia 1280 (Pal, B1 - int. 10) 1 - 00189 Rome, Italy
Phone: (+39) 30361612 Fax: (+39)30361612 E mail: crigusti@tin.it